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Arbeit unter wissenschaftlicher Betreuung von
Dr. Salim E. Darwiche, PhD

Rotator Cuff Repair: An analysis of failure mechanisms and predictors of structural and clinical repair outcomes

Inaugural-Dissertation

zur Erlangung der Doktorwürde der
Vetsuisse-Fakultät Universität Zürich

vorgelegt von

Philipp A. H. Kindt

Tierarzt
von Worpswede, Niedersachsen, DE

genehmigt auf Antrag von

Prof. Dr. Brigitte von Rechenberg, Referentin

Prof. Dr. Stephen J. Ferguson, Korreferent

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Meinen Eltern
in Liebe und Dankbarkeit

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Zusammenfassung

Post-operative Re-Rupturen stellen die wohl grösste Herausforderung bei der chirurgischen Versorgung von Rotatorenmanschettenrupturen dar. Inwieweit diese Re-Defekte klinische Relevanz haben, wird derzeit kontrovers diskutiert. Diese Dissertation untersucht mögliche Mechanismen, welche zur Entstehung von Re-Defekten führen. Um die klinische Relevanz dieser Mechanismen zu bewerten, das Verhältnis von strukuturellem und klinischem Operationsergebnis zu untersuchen und mögliche Ergebnisprediktoren zu identifzieren, wurde eine Meta-Analyse von 31 klinischen Studien durchgeführt.

Die Daten dieser Analyse bewiesen, dass auch in Patienten mit post-operativer Re-Ruptur, eine signifikante Verbesserung klinischer Symptome erzielt wird. Jedoch zeigte der Vergleich der Daten re-rupturierter und intakter Sehnen, einen statistisch signifikanten Unterschied zu Gunsten post-operativ intakter Manschetten.

Hinsichtlich predominanter Fehlermechanismen konnte die Analyse klinischer Studien nur begrenzt Aufschluss geben. Nach Zusammenfassung der klinischen Daten, sowie den Ergebnissen einer generellen Literaturrecherche, konnten bestimmte Problemzonen heutiger Behandlungstechniken identifiziert werden.

Abschliessend wird ein ovines Manschettenmodel präsentiert, welches in erster Linie die Untersuchung einer post-operativen Lückenbildung zwischen der re-inserierten Sehne und ihrem knöchernen Ursprung ermöglicht. Zudem erlaubt es die Untersuchung genereller Aspekte der Heilung reparierter Manschetten.

Summary

Post-operative re-tearing represents a major challenge in the surgical treatment of rotator cuff tears. Whether or not re-torn cuffs inevitably cause inferior clinical outcomes is temporarily a subject of controversial debate. This thesis investigates the occurrence of rotator cuff re-tearing by analyzing the repair components of current surgical concepts and discussing potential failure mechanisms. In order to evaluate the clinical relevance of these mechanisms, investigate the relation of structural repair failure and clinical outcome and furthermore identify predictors of structural and clinical outcome, a meta-analysis of 31 studies (3611 shoulders in total) was performed. The data showed significant relief of clinical symptoms and an increase in shoulder function in both, patients with intact repairs and those showing cuff re-tears. However, it also confirmed a correlation between re-torn cuffs and generally lower clinical results. The meta-analysis of patient, surgical, imaging and clinical follow-up data could only very limitedly provide information about the underlying mechanisms of failure. When synthesizing results from the clinical study meta-analysis and general research including animal and ex-vivo studies, several hot spots in current concepts were identified. Finally, an ovine model is presented that allows further investigation of repair site gap formation and assessment of general aspects and timing of rotator cuff healing.

1 Introduction

1.1 Purpose of thesis

Rotator cuff tears represent a major indication in orthopedic surgery. Despite decades of intensive research, the repair of torn cuffs remains a surgical challenge. Re-tearing of repaired cuffs is a frequently observed complication and, despite all accumulated knowledge and technical progress, re-tear rates are still significant.

The purpose of this thesis is to thoroughly analyze possible mechanisms that cause structural failure (re-tearing) of current rotator cuff repair concepts, evaluate the clinical relevance of those mechanisms and subsequently develop an animal model that can help investigate repair failure.

1.2 Thesis structure

To understand the pathology of rotator cuff tears and explain the challenges of surgical treatment, the first chapter of the thesis will give an anatomical and pathological background and outline the surgical rationale. Then, current surgical concepts will briefly be presented and subsequently dissected into their repair components, which at the same time reflect potential failure foci. The mechanisms leading to failure will be presented for each component and their relevance will be critically discussed.

After investigating and discussing the failure mechanisms in theory, in the second part of this work, the data of 31 clinical studies is compiled and analyzed in order to identify hints of predominating failure mechanisms and further understand the relation in between the structural and the clinical outcome after surgery. Furthermore a random effects model was designed around the data in order to test the ability of disease and treatment related factors to predict the structural and functional outcome after rotator cuff repair.

Finally, in the last chapters the results will be critically discussed and an animal model will be presented that allows further investigation of fundamental repair components.

2 Background

2.1 Anatomy and pathogenesis

The glenohumeral shoulder joint is designed to ensure a wide range of motion and to withstand strong repetitive forces without compromising stability. The rotator cuff is a fundamental component of this joint. It consists of four muscles connecting the scapula with the proximal humerus. These are the supraspinatus, the infraspinatus, subscapularis and teres minor muscle. By surrounding the humeral head in a cuff-like fashion, these muscles equally compress it to the glenoid, ensuring balanced acting forces through force couplings. The unique anatomical relationship between humeral head and glenoid resembles a golf ball sitting on a small tee. This picture emphasizes the strength and durability that the rotator cuff must provide in order to keep the humeral head in place and ensure physiological shoulder function.

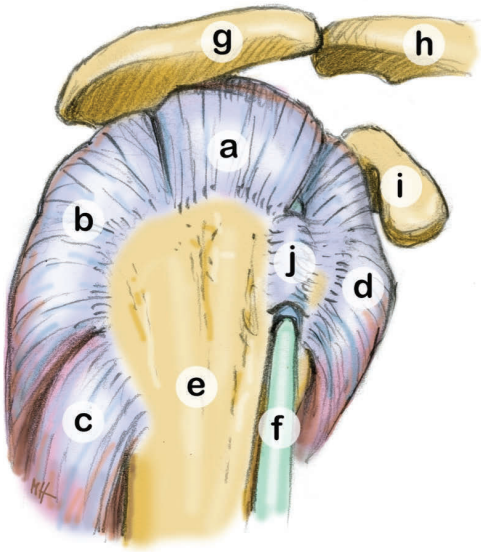

***Figure 2.1** (© M. Haab): Lateral view of the rotator cuff **(a-d)**, **a** supraspinatus tendon; **b** infraspinatus tendon; **c** teres minor tendon; **d** subscapulairs tendon; **e** proximal humerus; **f** biceps tendon with biceps tendon sheeth (j); **g** acromion; **h** clavicle; **i** processus coracoideus*

Rotator cuff tendon tears (RCT) are frequently observed injuries. Their clinical affection varies from an asymptomatic shoulder status to severe pain and shoulder

dysfunction. Tear size and duration play a major role in the extent of clinical affection. Associated clinical symptoms are primarily pain, weakness, shoulder instability and limited range of motion [1]. In severe cases this can include the inability to lift the arm above shoulder height.

Tear etiology is poorly understood. Both, traumatic and degenerative rotator cuff lesions may occur [2]. The two etiologies are not mutually exclusive, as degenerated cuffs may tear completely due to a minor traumatic incidence. Purely traumatic RCT is more often seen in younger patients [3] while degenerative RCT is age-related, predominantly affecting the elderly [4]. The etiology of RCT is multifactorial. Many intrinsic and extrinsic factors have been identified. Intrinsic factors include aging [5], poor vascularity [6], alterations in tissue properties [7], smoking [8, 9], hypercholesterolemia [10] and family history [11]. Extrinsic factors are subacromial impingement [12], acromion shape [13] and repetitive stress.

According to Yamamoto et al., the prevalence of full thickness RCT in people over 60 years of age is over 25% and in people over 80 years of age as high as 50% [14]. However, RCT are not always clinically relevant. Different numbers of asymptomatic tears have been reported, ranging up to 2/3 of all tears in an elderly population being asymptomatic [14-16]. Dominant shoulders are at a higher risk for rotator cuff lesions [14]. A higher incidence of rotator cuff injuries was also detected in populations with occupationally specific shoulder activity [16].

Yet RCT pathogenesis remains incompletely understood [17]. It is currently believed that the onset of a chronic rotator cuff tear originates with intratendinous microtears caused by the repetitive shear and compressive forces acting on both the articular and the bursal side of the tendon [13, 18]. These microtears multiply with time and the tendon's ability to resist forces gradually decreases. Force overload and imbalance in the remaining tendon likely causes further tearing and finally may result in a full thickness tear [19].

RCT etiology has also recently been linked to the critical shoulder angle or CSA [20]. That is the angle between a line through the inferior and superior aspect of the glenoid and a line from the inferolateral most edge of the acromion to the inferior aspect of the glenoid, measured from AP radiographs (Figure 2.2).

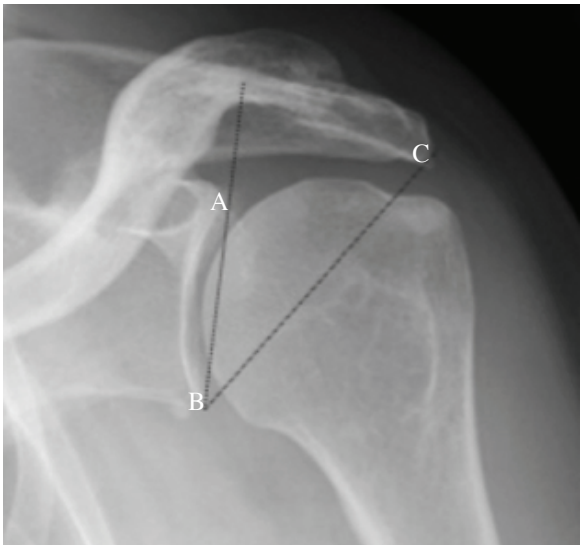

Figure 2.2: *Adapted from Moor et al. 2014. A/P radiograph of the shoulder. The CSA is measured between two lines drawn through these anatomic reference points:* ***A*** *superior border of the glenoid fossa;* ***B*** *inferior border of the glenoid fossa;* ***C*** *infero-lateral aspect of the acromion.*

Patients with RCT had a greater CSA compared with those of an asymptomatic control population. Osteoarthritic patients had a smaller CSA [20]. An uptilted glenoid in combination with greater acromial coverage of the glenohumeral joint, indicated by a greater CSA, was therefore correlated with a significantly higher prevalence of RCT. The anatomical circumstance described by a greater CSA may lead to decreased superoinferior joint stability, which is possibly compensated with higher activity of the supraspinatus muscle. Subsequently the load on the supraspinatus tendon may be increased in patients with greater CSA [21].

2.2 Rotator cuff tear characteristics

Tearing of the RCT occurs primarily close to the bony insertion of the affected tendons. A tear can be limited to one tendon but often affects multiple components of the cuff. Most isolated tears occur in the supraspinatus tendon [22]. However, involvement of the infraspinatus or the subscapularis tendon is frequently observed as well.

Different tear shapes have been described. The tear shape is related to the tear size and the extent of tendon retraction in combination with the force applied by the detached or

partially detached muscle [23]. Predominantly, tears have been described to be crescent and U-shaped as well as L-shaped or reversed-L-shaped. L-shaped tears involve a longitudinal affection of the tendon. Depending on their extent, L- and U-shaped tears may require side-to-side repair prior to cuff re-fixation. This means the longitudinal (mediolateral) tear component is closed with simple stitches. As this technique helps to reduce strain by creating a "new" tendon edge, it is also referred to as "margin convergence" [24].

A rotator cuff tear can affect the tendon as a whole or only partially. Partial thickness tears may occur at the bursal or articular side but can also be localized strictly intratendinous. A full thickness defect refers to the complete rupture of the tendon. Several classifications of the tear size have been described. DeOrio and Cofield measure anteroposterior tear dimension and distinguish between small (<1cm), medium (1-3cm), large (3-5cm) and massive (>5cm) tears [25]. On the other hand, Patte measures the mediolateral extent of a tear, defined by the retraction of the tendon edge away from the humerus in the coronal plane [26]. The mediolateral tear dimension is predominantly a function of myotendinous retraction. Patte differentiates three grades of tendon retraction: tendons still close to their original insertion and showing only very little retraction (Grade I), tendons with the torn edge at the level of the humeral head (Grade II), and tendon stumps that are retracted to the level of the glenoid (Grade III). This measurement is important in order to assess the mobility and with it the reparability of a tear. Further retracted tendons are difficult to reattach, as they have to be "pulled" to the footprint. This will cause pre-tensioning of the repaired tendon, which is likely to negatively influence its durability [27].

A full thickness RCT causes, depending on the duration of the condition, several myotendinous sequelae. By detaching and thus inactivating the affected muscle, full-thickness RCT can induce muscle atrophy and subsequently lead to fatty infiltration [28-30]. It is believed that the architectural changes within the muscle, precisely the fiber shortening related increase in pennation angle, leads to fatty infiltration by enabling adipocytes to fill the grown inter-myofibrillar space [30]. To assess the severity of fatty infiltration, Goutallier et al. proposed a classification system based on computed tomography (CT) [31]. The widely used system grades the extent of fatty infiltration by comparing the amount of fat with the amount of muscle on a 5-stage scale. Grade 0 is equivalent with the absence of fat, Grade 4 is characterized by more fat

than muscle tissue and Grades 1-3 reflect intermediate stages in between. Fuchs et al. validated the system for MRI [32]. Larger and long-standing tears tend to be correlated with higher Goutallier grades [33] and higher grades of fatty infiltration have been found to significantly increase the risk of rotator cuff re-tearing [34-36]. Therefore an early repair time point is preferable [37].

Another consequence of full-thickness tears is the retraction of the affected tendon itself, independent of the muscular retraction [38]. Independent shortening of torn (or generally detached) tendons has been explained with aberrant collagen fiber crimping and atrophy of collagen fibrils [39]. A quantitative analysis of the myotendinous retraction ratio identified muscle retraction to account for the major portion in this relationship. However, in more advanced stages of fatty infiltration (Goutallier 3 to 4) the effect of pure tendon retraction increases [40].

2.3 Repair rationale

While tears of the rotator cuff are not always symptomatic, they can however cause pain and severely affect shoulder functionality. There are approximately 4.5 million patient visits a year due to RCT related symptoms in the United States alone. Surgical treatments are estimated around 250’000 yearly [41]. This underlines the significant socioeconomic impact of RCT on both the young active and growing elderly population.

Conservative treatments including physiotherapy and local application of corticosteroids, hyaluronic acid and other agents have been reported to reduce pain and partially increase functionality in some patients [42, 43]. However, surgical treatment of RCT is needed in a large number of patients in order to restore satisfactory shoulder functionality and sustainably reduce pain.

RCT repair is designed to achieve re-fixation of the torn tendon to its original insertion site on the humerus, thereby ensuring the precondition for cuff healing. Nevertheless, many clinical series showed that also patients with structural repair failure clinically benefit from surgery [44-51]. By restoring cuff anatomy, surgical intervention is also the only adequate method to halt or at least decelerate degenerative changes in affected muscles [52].

2.4 Challenges of rotator cuff repair

The fundamental RCT repair rationale, however, faces critical biomechanical and biological challenges. The great forces that act on the vulnerable repair site easily overstress the repair components even after slow and careful patient rehabilitation. Re-tearing of repaired tendons has been a complication observed since the origin of surgical treatment of rotator cuff injuries. Cuff re-tears can be diagnosed with any major imaging technology. Magnetic Resonance Imaging (MRI) and Ultrasound assessments of the repair site are more common than Computed Tomography (CT) scans. A recurrent defect can present as a focal affection of the repair site or involve complete detachment of the repaired tendon. A five-stage classification by Sugaya [53] proposes a standardized system to evaluate postoperative tendon integrity with MRI. In this system "Sugaya type I" is a repaired cuff that shows sufficient thickness with homogeneously low intensity on each image. Type II refers to sufficient cuff thickness associated with a partial high-intensity area. Type III relates to insufficient thickness without discontinuity. In Type IV, the presence of a minor discontinuity in more than one slice of each image indicates a small tear. Finally, type V is the presence of a major discontinuity on each image, representing a medium or large tear. Type I-III MRI findings are considered to reflect intact cuffs. In cases of type IV and V imaging, the diagnosis of a re-torn cuff is justified [54].

The rate of general perioperative complications has nevertheless decreased with the evolution from open to all-arthroscopic procedures [55]. However, re-tearing is still a major concern after rotator cuff repair and accounts for the vast majority of complications [56]. After analyzing over 8000 arthroscopic rotator cuff repairs from multiple clinical studies, McElvany et al. reported an average re-tear rate of 26.6% within less than 2 years postoperatively [57].

Although initial repair strength and durable repair integrity have been identified to be important preconditions for structural healing of repaired cuff tears, improving biomechanical properties of repair constructs could not yet reduce structural failure rates significantly. This emphasizes the importance of the biologic component in the complex of tendon repair. Indeed, biomechanically optimized concepts can only partially translate into optimized tendon healing, as there is only a narrow threshold in between biological benefit and negative tissue affection. Healing failures can only be

avoided by optimizing both biomechanical and biological components of the surgical repair.

This thesis attempts to consolidate the experience the field of RCT repair has amassed throughout the evolution of repair technique and align it with the fundamental components required for successful repair. The resulting surgical and clinical drawing board is aimed to identify “repair hot spots” that need to be addressed with targeted research in order to generate new and more effective concepts for RCT repair.

3 Design of surgical repair

3.1 Surgical techniques

Throughout the history of rotator cuff repair, the most relevant innovation in surgical techniques was the evolution from open to arthroscopic procedures. Initially, issues in arthroscopic handling and tendon fixation made arthroscopic repairs inferior to open techniques. However, the continuous effort to enhance arthroscopic instruments and methods quickly resulted in similar outcomes, when compared with the open method [58]. Nowadays, the vast majority of rotator cuff repairs are performed arthroscopically. Additionally, many different concurrent procedures have been identified over the past decades as important contributors for successful repairs [59].

3.1.1 Open repair

For a long time, the open transosseus repair was considered the gold standard [59]. This technique can be performed with several approaches. Mainly, a delto-pectoral approach is chosen as it allows access through the delto-pectoral interval without deltoid detachment. The sutures are placed in the torn tendon, preferably with use of a modified Mason-Allen stitch. This locking stitch suture pattern has demonstrated superior holding strength in the tendon compared with other suture techniques [60]. Bone tunnels are drilled laterally and medially in the footprint area exiting distal-lateral at the greater tuberosity. The suture threads are pulled through the tunnels and knotted laterally over the greater tuberosity or augmentation devices. Advantages, disadvantages and major variations are presented in Figure 3.1.

Advantages
- good accessibility of the tendon
- easier application of complex suture techniques
- no arthroscopy equipment required
- technically less demanding

Disadvantages
- large incision→ high surgical morbidity
- higher discomfort for patient
- low visibility of glenohumeral joint

Variations
- suture pattern (modified Mason-Allen, grasping techniques)
- fixation of suture threads (knotted over bone or augmentation plates)

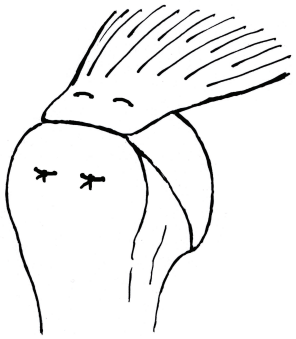

Figure 3.1 *(drawing by M. Haab): Schematic representation of a traditional transosseus rotator cuff repair. The sutures are guided through bonne tunnels to the lateral aspect of the greater tubercle, where they are knotted.*

3.1.2 Mini-open repair

In 1990, the first arthroscopically assisted repair was described, the "mini-open" technique [61]. After diagnostic shoulder arthroscopy and debridement of tendon edges and cuff mobilization, the anterior-superior portal is slightly extended by 1-2cm and subsequently the deltoid is split longitudinally without detaching it from the acromion. This gives sufficient access to the torn cuff in order to perform secure tendon-to-bone fixation. Advantages of this technique include a less invasive approach than in open repairs, lower risk of wound healing complication and the initial arthroscopy allows proper decision-making. Disadvantages, however, include low accessibility to establish repair constructs and the need for arthroscopic instruments and skills.

3.1.3 Single row repair

After the first description of arthroscopic suture placement in the rotator cuff in 1993, the first all arthroscopic repairs were performed and developed quickly during the second half of the 1990s. Commonly, three to five portals are created to ensure sufficient visibility and accessibility. After cuff preparation and mobilization, one or more preloaded suture anchors are placed slightly lateral to or within the tendon's footprint. The sutures are then passed through the tendon in a simple stitch or mattress

fashion and knotted with enough tension to ensure sufficient tendon-to-bone contact. Advantages, disadvantages and major variations are presented in Figure 3.2.

Advantages
- minimal invasive→ reduced surgical morbidity
- enables to explore glenohumeral joint
- fast to perform, when trained

Disadvantages
- only one row of fixation points
- does not restore footprint well
- vulnerable to gap formation
- not recommended for all tear sizes

Variations
- position of anchors (more medial, more lateral)
- suture anchor number
- suture pattern and number

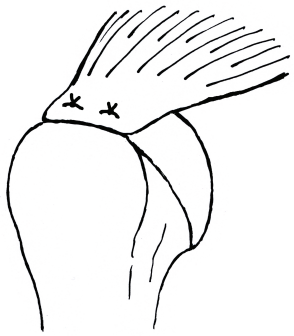

Figure 3.2 *(drawing by M. Haab): Schematic representation of a „single row" rotator cuff repair. One row of suture anchors is used to re-attach the torn cuff. In this case 2 anchors are used. Each anchor is loaded with 2 sutures that are passed through the tendon and knotted.*

3.1.4 Double row repair

The double row technique was first described in 2003 [62]. A second row of anchors was added to the concept of arthroscopic single row repairs to provide better footprint restoration and improve repair stability. The medial row of anchors is placed just lateral to the articular margin of the humeral head. After passing the medial row sutures, the lateral anchors are implanted lateral to the medial row and their sutures are passed through the tendon. Then first the medial sutures and subsequently, the lateral sutures are tied and knotted. The area of the footprint covered with tendon is significantly increased in comparison with single row repairs [63]. The double row re-fixation also provides higher initial fixation strength [64, 65]. Advantages, disadvantages and major variations are presented in Figure 3.3.

Advantages
- benefits of arthroscopic repair (see single row)
- higher initial strength compared with single row
- less vulnerable to gap formation (two rows of fixation)
- good restoration of footprint

Disadvantages
- more material required, more affection of the tendon, longer time to establish repair, higher costs (compared with single row)
- possibility of medial re-tearing due to tendon overtensioning

Variations
- number of suture anchors per row
- suture pattern (mainly mattress fashion for the medial row, mattress or simple stitches at lateral row)

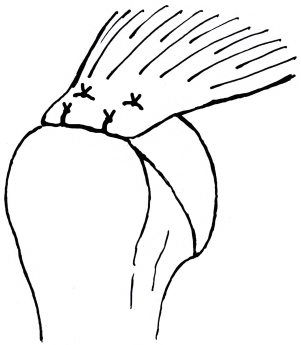

Figure 3.3 *(drawing by M. Haab): Schematic representation of a „double row" rotator cuff repair. Tendon reattachment is performed with 2 rows of suture anchors. One medial, one lateral. In this case two double loaded anchors are used per row. Medial sutures are knotted in a matress fashion. Lateral sutures are fixated with a simple stitch.*

3.1.5 Suture bridge repair

In 2006, Park et al. optimized the conventional double row repair by interconnecting the medial and the lateral row [66]. After placing the medial anchors, suture passing and tying, the remaining suture limbs are not cut but spanned over the tendon edge and tied with the lateral row of anchors which is placed distal-lateral at the greater tuberosity. That way the suture limbs that interconnect the rows compress the tendon to the footprint. This technique somewhat mimics the original open transosseus technique and thus is also called transosseus equivalent repair. Several ex vivo studies showed biomechanical superiority of this technique [67-69]. It provides optimal footprint restoration and shows high initial repair strength and furthermore optimizes tendon-bone contact, which is believed to be essential for tendon healing. Advantages, disadvantages and major variations are presented in Figure 3.4.

Advantages
- highest footprint congruency
- provides compression of tendon onto footprint
- high initial repair strength
- high ultimate load to failure

Disadvantages
- rigid construct
- high amount of medial re-tearing
- possibility of tendon overtensioning

Variations
- number of anchors
- design of suture bridge
- anchor type (knotless)
- design of medial row (knotted or knotless)

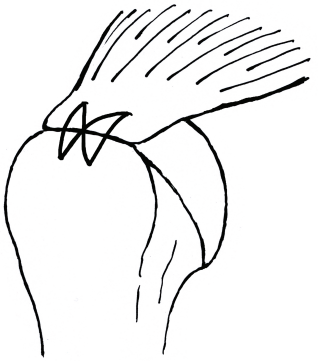

Figure 3.4 *(drawing by M. Haab)**: Schematic representation of a „transosseus equivalent“ or better „suture bridge“ repair construct. In this technique two rows of suture anchors are implanted, the sutures from the medial row are spanned over the tendon edge and fixated at the lateral anchor row.*

3.2 Postoperative rehabilitation

Independent of therapy method, after surgery, the repair has to be protected and the affected shoulder must be adequately rehabilitated. Early protection of the repair from overload is essential. Thus the affected arm is placed in an immobilization sling immediately after the operation. Time of immobilization and also position of the arm in terms of abduction degree may vary as well as the timing of various exercise stages. Generally rehabilitation protocols consist of 3 phases. An immobilization phase, followed by first passive and later active range of motion (ROM) exercises and finally gradual strengthening exercises.

Two major and per se conflicting goals have an influence on the design of postoperative rehabilitation protocols after rotator cuff repair. One is the protection of the repair construct from excessive loading with an adequate immobilization period and prevention of early mechanical failure until sufficient tendon healing takes place. The other favors the earlier onset of shoulder exercise or shorter immobilization and active ROM phases in order to avoid postoperative shoulder stiffness and regain functionality

quickly. Both concepts tackle important aspects of postoperative patient rehabilitation and are important to consider when designing patient-specific rehabilitation protocols.

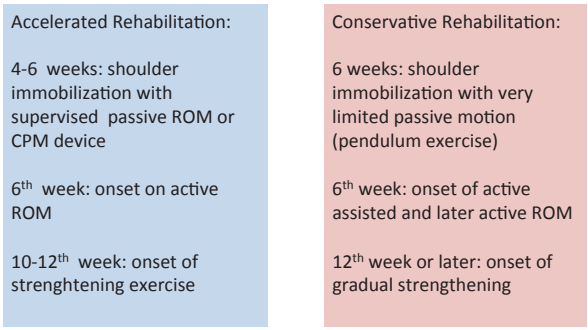

***Figure 3.5**: Examples for an accelerated and a conservative patient rehabilitation protocol after rotator cuff repair.*

In their comparison of two protocols, Lee et al. found a re-tear rate more than twice as high in patients with an accelerated rehabilitation approach [70]. The difference between the groups was not statistically significant because the study was underpowered. However, a strong trend shows that accelerated, relatively aggressive protocols are more likely to harm the repair than slower, conservative concepts with extended time of shoulder immobilization. Bigliani et al reported in their RCR revision series 5 of 31 re-tears to be correlated with physical therapy [71]. Two recently conducted meta-analyses with the purpose of finding significant differences in between different rehabilitation protocols both found statistically significant influence of pre-operative tear size [72, 73]. That is, large tears have a higher risk of re-tearing when rehabilitated with an accelerated protocol. For small tears however, Kluczynski et al found a statistically significant benefit of early mobilization with regard to tendon healing [72]. A combination of both concepts in terms of an individually matched protocol based on patient history, tear characteristics and treatment is likely to be the most promising approach to adequate rehabilitation after rotator cuff repair.

3.3 Defining the fundamental components of repair

The main goal of a rotator cuff repair is the re-fixation of the torn cuff to its humeral insertion. This sounds fairly simple but a repair construct is a complex structure, relying on multiple components. In the process of analyzing RCR re-tearing, dissecting the

fundamental components of rotator cuff repair is crucial in order to understand potential failure mechanisms. Fundamental components of rotator cuff repair are represented and described in Figure 3.6.

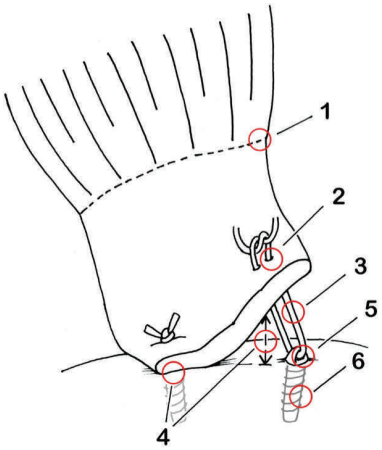

***Figure 3.6** (© M. Haab): Fundamental components of repair. Schematic representation of a rotator cuff tendon re-insertion with suture anchor fixation. The repair consists of the following fundamental components: (1) The tendon (with musculotendinous junction), (2) The suture-tendon interface, (3) The suture, (4) The tendon-bone interface, (5) The anchor-suture interface and (6) The anchor-bone interface. All six components are fundamentally important to ensure the success of surgical rotator cuff repair.*

Depending on the technique (open vs. arthroscopic) these components vary slightly. The traditional open technique lacks components 5 and 6. It achieves re-fixation of the tendon without suture anchors as described above.

While rotator cuff repairs may be summarily dissected into these fundamental components, the individual components also constitute potential failure locations. Indeed, every one of these six fundamental components of repair may be simultaneously a component of failure. Identifying the weakest link will shape the engineered surgical repairs in the future.

3.4 Failure mechanism analysis

A failure after rotator cuff repair generally refers to a loss of repair integrity. Whether this repair failure is equal with the term of “complication” can be discussed critically since the majority of “re-torn” patients still benefit from surgery. In fact, many studies

were not able to detect statistically significant differences between patients with intact and those with re-torn cuffs in clinical post-operative scoring [48-51].

Approximately every fourth patient is subject to cuff re-tearing after RCR [57]. There are many terms used in the literature to describe this structural repair failure. It is generally indicated by the detection of a tendon discontinuity after rotator cuff repair in imaging follow-up. Failures are identified as “re-tear” [36, 45, 74], “recurrent defect” [75, 76], “persistent defect” [46, 74], “structural failure“ [46, 77] and other nomenclature. Though all references to failure share the same meaning, that is a recurrent discontinuity of the cuff after re-fixation, there are many mechanisms that can describe the underlying cause. Clinically, the differentiation between failure mechanisms is limited and only biomechanical ex-vivo or animal studies allow detailed insight into these mechanisms. While ex vivo biomechanical results are indeed clinically relevant, the clinical translation of these results must be carefully considered, especially because these studies lack the component of in-life metabolic processes. Animal models are powerful research tools because they allow the inclusion of in vivo aspects. However, the differences of animal tissues to human tissues need to be considered. In the following, potential failure mechanism at the different repair components will be discussed with regard to results from current non-clinical but also clinical literature.

3.4.1 Component 1: The tendon

A recurrent defect can occur either at the repaired footprint area or it can occur at a more medial aspect of the tendon that was not directly affected by the previous tear. With double row repairs and even more with the transosseus equivalent or suture bridge technique a different re-tear pattern has been described that was rarely seen in earlier repair methods [78, 79]. When imaging modalities as MRI and Ultrasound show a discontinuity of the repaired tendon with remnant tendon tissue at the footprint, this unambiguously points to a medial defect in an area of the tendon that was considered intact at the time of surgery. Since Cho et al. were the first group to evaluate and quantify this re-tear pattern, it is also referred to “Cho type 2 failure” in the current literature.

The tendon tearing medial to the repair site may point to (1) a stable but overly rigid repair with an associated shift in mechanical loads, (2) an affected and altered tendon tissue quality following the initial tear and (3) a weakening of the tendon tissue directly

caused by the repair construct. Most likely a combination of all three factors causes medial failure. However, especially the last point is interesting, as it seems there are two sides to the concept of compressing the tendon onto the bone. In theory the increase in repair strength and subsequent gapping resistance will optimize the tendon to bone healing potential. Practically however, there are hints that this high strength concept might compromise the tendon and potentially impedes healing rather then accelerating it. It has been described that the use of knotless suture techniques for the medial row was related with significantly less medial re-tearing [80, 81], indicating that a tightly knotted medial row has the potential to weaken the tendon. But the high incidence of medial failure might as well derive from the suture bridge that amplifies tension at the medial row and thus possibly compromises blood supply.

Investigating the tendon blood flow after different repair methods with the help of Laser Doppler Flowmetry in sheep, Liem et al. found that rotator cuff repair, regardless of method, significantly compromises tendon blood flow [82]. This may partially explain the occurrence of medial re-tearing, as the suture bridge configuration affects a large area of the tendon. Following this idea, Kim et al. histologically and biomechanically compared the healing site of a suture bridge repair and the traditional transosseus repair in a rabbit model [83]. They found that the suture bridge configuration histologically showed inferior vascularization of the healing site and an increased amount of tendon degeneration markers. Additionally, biomechanical testing revealed a significantly higher prevalence of medial tearing for the suture bridge group at 2 weeks after the repair. Tendon blood supply is basically ensured proximally through the musculotendinous junction, the connective tissue surrounding the tendon and reverse flow from the attachment site at the bone [84, 85]. For a freshly repaired rotator cuff tendon, the supply can only come from the proximal flow from the MTJ. If this blood supply is compromised because of a tightly spanned suture bridge, tendon degeneration with subsequent healing failure is a logic consequence.

Medial re-tearing seems to be a considerable mechanism of structural failure. Its extent is assessable in clinical studies, however the predominantly underlying causes need further investigation.

3.4.2 Component 2: The tendon- suture interface

The interface between the suture and the tendon tissue is a crucial component of the repair. Its effective area depends on the stitching pattern (number of stitches through tendon), the suture diameter and the tendon thickness. Many different tendon stitches have been analyzed for their performance in terms of tissue holding. More complex suture patterns lead to better anchorage in the tendon [86] but at the same time cause more intratendinous damage by a greater number of passages and thus affect a greater amount of tissue [87]. Subsequently, less complex suturing techniques cause less tissue damage but also possess worse anchorage properties and higher cut-through potential. Single row repairs are more vulnerable to cut-through than double row techniques [65].

The mechanism of the suture cutting through the tendon is also called “cheese wire mechanism”. Cummins et al. found in their RCR revision series that 19 of 22 repairs had failed because of the suture pulling (cutting) through the tendon [88]. This mechanism can either lead to immediate failure in terms of a complete cut through or if the suture does not cut the tendon all the way, it leads at least to repair loosening by disintegrating the suture-tendon interface and subsequently also the tendon- bone interface. This mechanism is tension-dependent and a correlation has been identified with suture material properties. Several laboratory studies investigated the biomechanical behavior of high strength suture materials in tendons and found significant differences in the performance of the most frequently used size 2 high strength sutures [22, 89, 90]. Although all currently used sutures are considered to provide sufficient ultimate strength, in terms of stiffness, knot security and especially abrasive properties there are great variations in between materials. Particularly lower coefficient of friction and higher stiffness of a suture material have been found to be correlated with significantly increased abrasive character and therefore as well with higher potential of cheese wiring a tendon [22]. But also the tendon tissue quality has an influence on the appearance of cheese wiring. That means a degenerated tendon is less resistant to mechanical disturbance than a freshly ruptured but non-degenerated one [91]. Chung et al confirmed in their case series of arthroscopically repaired small full thickness and high-grade partial thickness RCT a significant correlation between the grade of tendinosis and the re-tear rate [49]. This might indicate both, a higher vulnerability to cheese wiring and/or a generally diminished healing potential of tendinosis affected tendons.

Furthermore the location of the stitches in the tendon has been found to influence the impact of cheese wire mechanism at the suture-tendon interface. Wieser et al. reported that stitching just medial to the rotator cable, a thick bundle of fibers that run perpendicular to the supraspinatus tendon axis, provided superior tissue holding of the suture and decreased cut out compared to other stitch locations [92].

3.4.3 Component 3: The suture

The suture itself, acting as the link between bone and tendon, can break and subsequently cause failure [93]. However, with the introduction of sutures made of ultra high molecular weight polyethylene (UHMWPE), suture breakage as a mode of failure in rotator cuff repair seems to be eliminated. But still, currently available materials are not optimal and other suture related failure mechanisms remain to be relevant. These are the effects of knot seating and suture slippage (creep).

Neuhofer et al. have shown that knot seating (the process of the knot tightening post-operatively when it is exposed to strong forces – and as the knot tightens, the suture string elongates), can cause several millimeters of elongation in a suture, regardless of the tying force that a surgeon is able to apply [94]. Also the knotting technique influences the extent of this process [95]. Currently used sutures provide high stiffness. However, when strong forces are applied the new materials still lengthen to some extent resulting in suture creep [96]. Even though these processes only cause several millimeters of elongation, in combination and dependent on the applied load they can potentially cause an effect. Elongation of the suture subsequently leads to loosening of the repair and depending on the extent, this can result in a loss of contact between the tendon and the footprint area.

3.4.4 Component 4: The tendon-bone interface

The tendon- bone interface is basically the product of the repair. All techniques aim to create a solid contact area of the tendon edge and its anatomic insertion area on the proximal humerus in order to pave the road for tendon to bone healing. Except for medial re-tears, every other failure of one of the described repair components will show an effect at the tendon-bone interface by causing a decrease or total loss of contact here. This can occur in a rapid, excessive way, for example the suture cutting all the way through the tendon, resulting in immediate failure as described above. But it can also occur in a chronic manner, for example due to steady suture elongation and tendon

tissue creep. In this case the repair integrity might not be lost completely but a small gap arises between the tendon and the bone. Again, if this gap formation is excessive it is equal to an immediate (mechanical) failure because it cannot be “bridged” by the healing process. However, if the gap in between tendon and bone is small enough for the healing process to take place, there is still a high risk for the formation of poor quality repair tissue [97]. The biomechanical strength of this repair tissue is subsequently reduced and there is a high chance for re-tearing of the healed area once load is applied. In this case the proper term would be “healing failure” rather then “mechanical failure”, although mechanical insufficiency was the precursor of inferior healing. In fact, these etiologies of repair failure cannot be clearly separated. However, assuming that there was no gap formation at the tendon-bone interface, “pure” healing failure might still occur since the healing process depends on a variety of patient-specific factors. For example it was shown that diabetic patients, especially those with uncontrolled hyperglycemia, have lower tendon healing rates [98]. Also the tendon condition may compromise the healing potential [49].

Whether gap formation predominantly inhibits healing by an excessive extent or rather impairs the healing process with the subsequent result of inferior tendon repair tissue is yet unknown. A question that comes up with this is: What gap size is critical for successful healing? Gelberman et al. found in their investigation of critical gap width in between tendon edges of flexor tendons in dogs that a gap above 3 mm is wide enough to impair the healing process significantly [97]. This finding is very interesting as it is only a very narrow gap that seems to be bridgeable with resilient repair tissue.

To the knowledge of the author, only little investigation has been done at this time point to clinically assess the extent and frequency of gap formation at the tendon-bone interface. In their radiostereometric assessment of rotator cuff repair integrity, Baring et al. found that gap formation affected every repair [99]. They marked the greater tuberosity with tantalum beads and placed steel sutures in the repaired tendon at a defined distance in 10 patients. Measuring the distances in serial radiographs post-operatively they found an increase of the intra operative distance between the markers in 9 of 10 patients. In patients with an intact repair, as detected with ultrasound imaging, the distance increased to a smaller extent than in cuffs with recurrent defects. Interestingly, there was only very little marker movement in the very early postoperative period (0 to 3 weeks) in all patients. The next time point was set at 12

weeks and showed a significant increase of the distance between the markers in all but one patient. This patient was later considered to have a medial re-tear, which explains this result. An important finding to note is that as long as the shoulders were immobilized post-operatively, there was hardly any distance increase, indicating no gap formation during this time. After 4 weeks, the rehabilitation protocol demanded first passive assisted range of motion exercises and after 10 weeks the patients commenced full active movement. Unfortunately, no radiographs were taken in between 3 weeks and 12 weeks to detect an increase in marker movement right after the immobilization period. However, the results suggest that patient movement and with it loading of the repair, induces gap formation. The underlying mechanism however could not be assessed in this set up.

The many mechanisms (cheese wiring, suture and knot related disintegration etc.) contributing to the appearance of gap formation all share the important co-factor of tension. Thus, an important precondition for successful re-fixation is the adequate mobilization of the affected tendon(s) in order to prevent or at least reduce the preloading on the repair [100]. This will help to minimize tension that will inevitably occur during the graded rehabilitation phase (unintended patient movements, compliance issues, aggressive rehabilitation protocols). As mentioned above, especially in long existing cuff tears, retraction of the affected muscle and tendon is a frequently observed condition. Subsequently, tension free re-fixation is not always achievable and, in these heavily retracted tendons, reattachment will inevitably cause a preload. It can be assumed that these cases are more vulnerable to gap formation than sufficiently mobile cuffs.

To assess the impact of passive tension on gap formation, Reilly et al. first investigated the role of arm positioning [101]. In 5 patients with pre-operative tendon retraction of 20mm, they found that 30° of (passive) abduction reduced the tension in the repaired supraspinatus tendon by a mean of 34 N compared with the 0° abduction position. Then they applied this exact force for 24 hours to cadaver cuffs repaired with the same technique. Although the repair was performed with modified Mason-Allen stitches, which were identified as the most resistant suture pattern [87], the consistent force of 34 N lead to a mean gap formation of 9mm. According to the findings of Gelberman et al. as described above, a gap of 9 mm is considered very critical and most likely to inhibit tendon healing. Although those figures are certainly very dependent on tear size and

tendon retraction, they still show impressively the impact of the arm position on tendon tension. This finding emphasizes the importance of individual rehabilitation as it suggests passive abduction to be a very efficient way to reduce tendon tension in retracted RCTs postoperatively.

The factor of time also plays a major role in the complex of gap formation. Mechanical stability must be maintained until tendon healing has reached a point where it can compensate a potential loss of repair strength.

Furthermore the technique of fixation appears to have an influence on the extent of gap formation. Two studies that assessed and compared the biomechanical properties of single row and double row techniques found (among other parameters) that resistance to gap formation was significantly lower in a single row repair construct [102, 103].

Summing up all the described factors, the role of gap formation as a mechanism of failure or as a major precursor of healing failure is important. Indeed, while much effort has been invested in the limitation of gapping, it stays a major issue in rotator cuff repair.

3.4.5 Component 5: The suture-anchor interface

In the early days of suture anchor re-fixation, suture abrasion at the anchor eyelet has been described [104, 105] and moreover seemed to be a considerable mechanism of failure. However, with the introduction of UHMWPE high strength sutures and revised anchor eyelet design, this mode of failure became less prevalent.

Another suture-anchor interface based failure mechanism is the suture slippage in knotless anchors, which recently have gained popularity. These anchors allow re-fixation without the time consuming process of knot tying, thus potentially making tendon repair faster and less technically demanding [106]. Knotless anchors are mainly used for lateral row fixation in suture bridge repairs. They function by clamping and locking the suture limbs in different ways (between thread and bone, between inner and outer anchor components, etc.). The force that is able to cause suture slippage was found to be significantly lower than the force that is necessary for complete anchor pull out [106]. While this mode of failure may be clinically relevant, the role of suture slippage from knotless anchors as a mode of failure however, is difficult to assess in the setup of clinical studies.

3.4.6 Component 6: The anchor-bone interface

With the advancement of arthroscopic rotator cuff repair, the development of suture anchors has been significant. In 1991 only five types of anchors from 3 different manufacturers were commercially available [107]. Nowadays, more than a hundred anchors from multiple manufacturers are on the market [108]. In the early days of arthroscopic repairs, several anchor-related issues were identified. The first products were all metal anchors. Anchor pull out, breakage, migration, poor osseointegration and foreign body reaction are all complications that have been identified with suture anchors [109]. The insertion angle was detected to be an important factor for sufficient stability [110]. Also bone condition is an important factor to take into consideration when it comes to anchor holding and osseointegration potential. In fact, lower bone mineral density has been found to correlate with lower pull out strength [111]. That means osteopenic and osteoporotic bone is more vulnerable to anchor failure. However, with two decades of intensive research and steady progress in material properties and anchor design, anchor related failures have temporarily been limited to a very low incidence [56]. With the advent of anchors made from biodegradable materials, metal anchor associated disadvantages as retained hardware, difficult revision procedures and magnet resonance as well as radiologic imaging disturbances have been countered [106, 109, 112]. Earlier complications like accelerated degradation and disintegration associated inflammatory response have been reduced with optimized polymer characteristic designs [108, 113]. Also, biostable polymers have been introduced to avoid potential degradation related complications and simultaneously avoid the mentioned metal anchor related issues. Although current anchors have different osseointegration potential and use various anchorage techniques, pull out strength no longer poses a major problem nowadays. A recent clinical trial assessed the influence of anchor material on outcomes but has not found significant differences in between currently available anchors from either material [112].

With anchors and sutures having progressively improved in strength and durability over the past years, it seems the tendon has become the weakest link in current RCR concepts. After reviewing and discussing potential locations of failure, the tendon itself and its interfaces with the suture and the bone indeed reflect the most vulnerable links in current rotator cuff repairs. A detailed analysis of clinical trials will follow in order to potentially confirm this assumption clinically.

4 Methods

4.1 Selection of studies

A literature search was conducted on the Pubmed database. Search terms such as "rotator cuff", "repair", "failure", "arthroscopic" and combinations thereof were used to identify potentially relevant studies. The search results were then screened for their congruence with the following inclusion criteria: clinical trial or series of any evidence level, publication date from 2005 until 2015, written in English, sample size ≥ 20 shoulders, only arthroscopic procedures, no revision series, reporting on structural outcomes assessed with any modality of medical imaging (Ultrasound, Magnet Resonance Imaging or Computed Tomography). Also, some of the included studies were found searching the bibliographies of previously included studies. If a study met all inclusion criteria, the assessment and reporting of certain parameters within the study was analyzed as described below and the data was collected. The search was conducted systematically following these guidelines in order to compile a representative, albeit not exhaustive, list of included studies for statistical analysis.

Generally, two types of studies were included: Clinical series with only one patient group and clinical trials comparing multiple patient groups according to different treatments (surgical treatment or rehabilitation protocols). Patient groups from the latter studies were reported separately in our dataset. Parameters reported only as overall population parameters and not specifically for each treatment group were included in our dataset with the assumption that the overall parameter value described the individual treatment groups as well.

4.2 Analyzed parameters

Studies were catalogued and relevant data was collected for the following parameters: publication year, patient recruitment years, number of shoulders, patient age, gender distribution, repair method, suture material, anchor material, rehabilitation stages, imaging method, imaging time point, clinical follow-up time point, pre-operative and post-operative clinical scores (Constant, ASES, UCLA), pre-operative and post-operative VAS grading for pain assessment, re-tear rate and medial failure rate (Cho Type 2 Failure).

First Author / Year	PG	Country	LoE	Journal
Anderson / 2006 [46]	PG 1	USA	4	Am J Sports Med
Carbonel / 2012 [114]	PG 2, 3	Spain	1	Int Orthop
Cho / 2011 [36]	PG 4	S. Korea	4	Am J Sports Med
Cho / 2015 [98]	PG 5	S. Korea	3	Am J Sports Med
Choi / 2014 [45]	PG 6	S. Korea	4	J Shoulder Elbow Surg
Chung / 2014 [49]	PG 7	S. Korea	3	Am J Sports Med
Deutsch / 2008 [77]	PG 8	USA	3*	J Shoulder Elbow Surg
Flurin / 2013 [47]	PG 9	France	3*	Orthop Traumatol Surg Res
Frank / 2008 [48]	PG 10	USA	4	Am J Sports Med
Iannotti / 2013 [74]	PG 11	USA	4	J Bone Joint Surg Am
Keener / 2014 [115]	PG 12	USA	1	J Bone Joint Surg Am
Kim K / 2012 [50]	PG 13	S. Korea	4	J Bone Joint Surg Am
Kim K / 2012 [116]	PG 14, 15	S. Korea	2	Am J Sports Med
Kim Y / 2012 [117]	PG 16, 17	S. Korea	1	Am J Sports Med
Koh / 2011 [118]	PG 18, 19	S. Korea	1	Arthroscopy
Koh / 2014 [119]	PG 20, 21	S. Korea	1	J Bone Joint Surg Am
Lafosse / 2007 [44]	PG 22	France	4	J Bone Joint Surg Am
Lapner / 2012 [120]	PG 23, 24	Canada	1	J Bone Joint Surg Am
Le / 2014 [121]	PG 25	Australia	3	Am J Sports Med
Ma / 2012 [122]	PG 26, 27	Taiwan	2	Arthroscopy
Miller / 2011 [123]	PG 28	USA	3	Am J Sports Med
Neyton / 2013 [75]	PG 29	France	4	Arthroscopy
Nho / 2009 [124]	PG 30	USA	3	Am J Sports Med
Park / 2010 [51]	PG 31	S. Korea	4	Clin Orthop Relat Res
Park / 2014 [125]	PG 32	S. Korea	3	Am J Sports Med
Sethi / 2010[126]	PG 33	USA	4	J Shoulder Elbow Surg
Sugaya / 2007 [54]	PG 34	Japan	4	J Bone Joint Surg Am
Tashjian / 2010 [127]	PG 35	USA	4	Am J Sports Med
Toussaint / 2011 [76]	PG 36	France	4	Am J Sports Med
Voigt / 2010 [128]	PG 37	Germany	4	Am J Sports Med
Zhang / 2014 [129]	PG 38	China	1*	Eur J Orthop Surg Traumatol

***Table 4.1**: Table shows the first author and publication year of selected studies, the assigned patient group number(s) (PG), the country where the research was performed, the level of evidence (LoE) and the publishing journal. An asterisk indicates an assumed LoE if the authors did not report it.*

Each patient group was given a code corresponding with an alphabetical order based on the study's first author's last name. The individually reported patient groups were referred to as PG1, PG2 and so on, up to PG38 (Table 4.1). If a study was designed to compare treatments and the data was reported independently per patient group, the paper data was reported separately. For example, Kim et al. [116] included two patient groups, which were reported in our dataset as PG14 and PG15. This kind of separate reporting was only possible if each patient group contained at least 20 shoulders, in line with our inclusion criteria. On the other hand, for instance, one patient group from the study by Cho et al. [98] was excluded because it was exclusively composed of hypoglycemic patients, demonstrating a clear population recruitment bias with respect to other patient groups. If reported, the year that the collection of patient data started and ended was recorded. This allowed the comparison of recruitment periods.

The sample size (the number of treated shoulders) per study was recorded. It is important to mention that the shoulder number did not always equal the patient number as some patients received bilateral treatment. Since the data collection within the studies occurred over a long period of time, some patients were lost to follow-ups. Some studies reported only on the number of shoulders for which they could provide a complete data set. However, other studies reported data for different shoulder numbers per parameter. For example, PG4 initially reports on 123 shoulders, but only 87 patients returned for the final follow-up. Therefore mean age, gender distribution, preoperative scores and surgical treatment data was reported for 123 shoulders while the mean re-tear rate and mean postoperative clinical scores reflected only data from 87 shoulders. In cases like this, we always took the number of follow-up patients (the smaller sample size number for a given patient group) as representative of the sample size for all parameters in that patient group. Although this method is not completely accurate, it is the more stringent assumption to be made as it presumes a smaller population to be predicted by mean values of a slightly larger population (The mean age from a set of 123 shoulders more accurately represents the mean age of the 87 shoulder subset than vice versa, assuming the 87 shoulders are a random sampling of the larger population). Patient age was also recorded as the mean age of a study population. The proportion of male to female patients within a study population was recorded to analyze gender distribution.

Three arthroscopic repair techniques were reported (TOE, DR, SR). The therapy method was reported as proportions of the three relevant techniques. For example, in PG16 and PG17, 82% of repairs were performed with the TOE technique, 2% with DR and 16% with SR. If more than one technique was used in one patient group but the numbers of patients treated with a specific technique was unclear, an equal distribution of the techniques was assumed. For example, in PG9, cuff repair was performed with DR or SR techniques but individual numbers were not reported. We then assumed that 50% of the cases were treated with a DR repair and 50% with a SR repair.

Suture material used for cuff repair was recorded. 5 different materials were found within the studies. Those were FiberWire® (Arthrex, Naples, FL, USA), Orthocord® (DePuySynthes, Raynham, MA, USA), Ethibond® (Ethicon, Somerville, NJ, USA), Ultrabraid® (Smith&Nephew, London, UK) and HiFi® (Conmed, Utica, NY, USA). If the suture material was not specifically mentioned, it could be often derived from the anchors that were used as most anchors come preloaded with sutures. The vast majority of cuff repairs were performed with FiberWire®. Thus suture material was recorded as proportion of FiberWire® versus alternate. If FiberWire® and another suture material were used without specifying numbers, an equal distribution was again assumed. For example PG11 used FiberWire® and Orthocord® for repair without reporting the specific patient distribution. We thus assumed 50% of the cases to be repaired with FiberWire®.

Various anchor materials were used in the studies. These could be generally categorized as bioabsorbable, metal and composite materials (e.g. biostable polymers and ceramic). For statistical analysis, the proportion of bioabsorbable anchors versus non-bioabsorbable per study was recorded. Again in the case of different anchor materials used in a study with unreported individual numbers, an equal distribution of two materials was assumed.

Detailed information about rehabilitation protocols was reported within the majority of studies, but in a non-standardized way. In order to be able to statistically utilize most of the reported data, the information was organized in categories. Two parameters were analyzed: The onset of active assisted range of motion exercise and the onset of strengthening (resistance) exercise. Two categories per parameter were chosen. The onset of active assisted ROM was either less than 6 weeks post-operatively (relatively accelerated) or equal or greater than 6 weeks post-operatively (relatively conservative).

Similarly, the onset of strengthening cutoff was set at 12 weeks with patients treated earlier in accelerated regimen and those treated later in a conservative regimen.

Ultrasound, Magnet Resonance Imaging or Computed Tomography were utilized to assess the structural outcome after surgery. For the most part, only one technique was used per patient group. A select few, however, mixed two techniques. For statistical use of the imaging information, we recorded the proportion of ultrasound assessment per study. If ultrasound and another technique were mixed and the numbers not adequately reported, we assumed an equal spread (50/50). The mean imaging time point was recorded in months. For studies that performed serial imaging, no mean time point was recorded as this would introduce a bias when analyzing a potential link between imaging time point and re-tear detection efficacy, especially if re-tear detection is not paired with a specific time point on a case-by-case basis. For studies that did not report on a mean imaging time point but mentioned imaging at a general time point postoperatively, this value was reported (e.g. When "Imaging follow-up was performed after 24 months" is indicated, we recorded 24 months as the imaging time point).

The re-tear rate per patient group was recorded as the percentage of patients within a patient group showing structural repair failure after surgery. When necessary, the re-tear rate may have also been converted to an effective number of re-torn shoulders per patient group. A few studies also assessed the location of failure if a tendon was re-torn. The percentage of medial failures, also known as "Cho type 2 failures", was also recorded.

Throughout the analyzed studies, several clinical scoring systems were used to evaluate the clinical affection of a shoulder. Most studies provided pre- and postoperative clinical scoring in order to evaluate clinical improvement after surgery. The three primarily used systems are the Constant score [130], the American Shoulder and Elbow Surgeons (ASES) score [131] and the University of Calfornia Los Angeles (UCLA) score [132]. For these three systems, we collected the mean pre- and postoperative results with their standard deviations if reported. In the case of PG16 and PG17, the standard deviations for score results had to be derived from the reported 95% confidence intervals. In PG2 and PG3, the score results separately reported by tear size group were combined in an overall value. When mean postoperative clinical scores were reported separately per structural outcome groups (intact cuffs vs. re-torn), here

also an overall score value was calculated from these two means and their standard deviations.

Additionally many studies used a Visual Analog Scale (VAS) to assess pre- and postoperative pain levels. The normal VAS for pain is a 10-point scale with “0” indicating no pain and “10” indicating worst pain. However there was also another scale used in the data set, where “15” indicated no pain and “0” indicated the worst stage of pain. In order to analyze and compare the VAS data, we inverted and transformed the 15-point scale to the 10-point scale.

The mean clinical follow-up time point was reported in months. If several clinical follow-up examinations were performed at several time points, the latest was reported. If the mean time point for a patient group was not reported, again we recorded the general value given for all combined patient groups in that study.

4.3 Omitted parameters

Additional parameters were analyzed and collected, even when they could not be statistically compared. Indeed, due to reporting differences, rarely reported parameters and definition discrepancies, many parameters describing the recruited population were not systematically reported and therefore were not used in statistical analyses in this report.

An example is the assessment of fatty infiltration of the cuff muscles. Many clinical series reported this measure when pre-operative imaging data was available. However, some reported fatty infiltration for one muscle only, others calculated the global fatty infiltration index from the three major cuff muscles and yet others only reported the overall cutoff fatty infiltration grade for patient inclusion (e.g. In PG36, patients with Goutallier grade 2 or below were included in the study).

The measure of tendon retraction with the Patte classification was also analyzed. Few studies specifically assessed and reported this measure, describing the spread of tendon retraction severity within their patient population. We presumed that studies, which did not specifically report Patte classification grades, did not present a bias in tendon retraction severity within their recruited patient populations. Nevertheless, it was not possible to statistically use this parameter in an adequate way from the few studies that reported it.

Furthermore the tear size often acts as an important baseline measure to describe the recruited patient population. Here again, there was no common reporting standard. A mean tear size was reported in some studies while others listed shoulder numbers per tear size categories. Due to these differences and sparse reporting, this parameter could not be statistically analyzed.

These three factors – fatty infiltration, tendon retraction and tear size – particularly influence and characterize the baseline condition of a study population. A population with predominantly higher fatty infiltration, larger tears and further retracted tendons is a higher risk population and would most likely show inferior outcomes compared to a patient group with an overall lower grade of fatty infiltration, smaller tears and less tendon retraction, given the same therapy and the same circumstances. Because it was not possible to use this baseline information in a reliable manner, any differences in structural and clinical outcome in between the studies have to be interpreted carefully. It is also important to note that, particularly because these three parameters fundamentally describe a patient population, the reliable and complete reporting of these measures is crucial in order to properly assess any reported clinical results in published clinical series. Table A 4.1 in the appendix shows the great differences in reporting of baseline parameters.

Some therapy related factors were also excluded from statistical analysis. For example the suture pattern or stitching technique was found to be the same in all studies that applied a suture bridge repair. The instances of single row simple stitch techniques and variations within double row repairs were scarce and therefore could not be worked statistically. Furthermore, concerning rehabilitation parameters, the duration of postoperative shoulder immobilization was also not analyzed statistically. While this parameter was regularly reported, we detected differences in the interpretation or definition of “immobilization”, with some studies strictly referring to the duration when no movement was allowed and other studies including passive Range of Motion exercises within the immobilization duration. These discrepancies in definitions are certainly detrimental when a systematic comparison of outcomes with respect to rehabilitation protocols is being conducted.

For every parameter that could be assessed statistically, the mean ± standard deviation and the ranges were calculated with the statistical software SPSS (Version 23, IBM Corp.). Descriptive statistics of each parameter were performed using individual means

of patient groups as opposed to individual patient-specific means as these data were not available.

4.4 Statistical population comparison (T-tests)

To detect the clinical benefit of surgical rotator cuff repair statistically, we compared the mean pre-operative and post-operative score results by performing Student's t-test using SPSS (Version 23, IBM Corp.). The test was performed for Constant, ASES, UCLA score and the pain VAS. The patient group data was weighed with respect to shoulder number.

A second t-test was performed, in order to detect statistical differences in the clinical outcome between patients that suffered a tendon re-tear after repair and those that presented intact tendons post-operatively. Only studies that reported clinical score results separately per outcome group could be included in this analysis (studies which reported clinical score data from re-torn and intact sub-groups separately). This comparison was performed for the Constant, ASES, UCLA score and for the pain VAS.

4.5 Meta-analysis: Random-effects model predicting re-tear rate

From the above-described parameters, many of which may influence the structural outcome of rotator cuff repair, we sought to identify the key modulators predicting re-tear rates and their respective effect sizes using a random effects prediction model in R Software (version 3.2.2, The R Foundation for Statistical Computing). To investigate the predictability of a re-tear, we set up a list of parameters that we either know to influence this outcome measure based on literature findings or that we would reasonably hypothesize may have an influence. The patient group data were weighed with respect to shoulder numbers and the following 10 parameters were tested for their predictive influence of re-tear rates:

1. Patient age
2. Gender distribution
3. Pre-OP clinical score results
4. Therapy (SR, DR, TOE)
5. Suture material
6. Anchor material
7. Onset of active assisted ROM exercise
8. Onset of strengthening exercise
9. Imaging modality
10. Imaging follow up time point

Within the R console, the “metafor” package for meta-analyses [133] was first loaded (code line 4.1). The data table was then imported in csv format (code line 4.2) and the “escalc” function was used to determine the outcome variable – in this case, the raw proportion (PR) of re-tears (xi) – and define the weighing by number of shoulders (ni) (code line 4.3).

```
library (metafor)                                                    (4.1)
data1<-read.csv("dataset.csv")                                       (4.2)
dat4y<-escalc(xi=re-tear, ni=shoulders, measure="PR", data=data1)    (4.3)
```

Where “xi” refers to the outcome variable, in this case the number of re-tears per patient group, “ni” indicates the sample size, in this case the number of shoulders per patient group and “measure “ indicates the type of outcome variable, in this case “PR” meaning “raw proportion”. As the number of re-torn shoulders represents in fact a subgroup of a given patient group’s shoulder population, the PR measure had to be chosen.

The “rma” function was then utilized to test the influence of the moderators (different parameters) on the defined outcome variable (re-tears) (code line 4.4).

```
res<-rma(yi,vi,mods=~age+as.factor(strengthening), data=dat4y)       (4.4)
```

Where yi= refers to the values calculated with the “escalc” function, vi= are the corresponding sampling variances and “mods” are the moderators (potentially influencing parameters). In the example above, the influence of age and onset of strengthening exercises on the re-tear rate is tested. The use of “as.factor” is needed in this case because the strengthening parameter was converted to a binary parameter indicating aggressive (0) or conservative (1) rehabilitation.

The statistics data table imported into the R console for meta-analysis is included in the appendix (Table A 4.2a and A 4.2b).

4.6 Meta-analysis: Random effects model predicting clinical scores

Similarly to the procedure above, we tested the influence of several parameters on the clinical outcome, indicated by the clinical score results. The parameters that were tested slightly differ from those taken into account for the re-tear model. The following were tested for their predictive influence of post-operative clinical score results:

1. Patient age
2. Gender distribution
3. Pre-op clinical score results
4. Therapy
5. Onset time point of active assisted ROM exercise
6. Onset time point of strengthening exercise
7. Clinical follow up time point
8. Re-tear rate

The “escalc” function had to be computed differently (code line 4.5). Indeed, the “measure” in the escalc function was changed to “MN”, which is the raw mean difference. This measure was selected because clinical scores, as outcome variables, are reported as means and standard deviations and do not refer to a number of shoulders, as it was the case with re-torn shoulders.

escalc(mi=ASESpost, sdi=ASESpostSD, ni=shoulders, measure=”MN”, data=data1) (4.5)

Where “mi” refers to the outcome variable, in this case the postoperative ASES score means, “sdi” refers to the outcome variable standard deviation, in this case the standard deviation of the ASES postoperative score means, “ni” indicates the sample size, in this case the number of shoulders per patient group and “measure “ indicates the type of outcome variable, in this case “MN” meaning “raw mean difference”. The “rma” function was then utilized similarly as with the re-tear rate prediction model (code line 4.4). The statistics data table imported into the R console for meta-analysis is included in the appendix (Table A 4.2a and A 4.2b).

4.7 Analysis of clinical scoring systems

Across the 31 clinical studies that were analyzed, 11 different scoring systems were used for clinical assessment. However, three scores were performed most frequently. As mentioned above, these were the Constant score, the American Shoulder and Elbow Surgeon (ASES) score and the University of California Los Angeles (UCLA) score. Other scoring systems utilized, were the Simple Shoulder Test (SST), the L’insalata questionnaire, the Western Ontario Rotator cuff (WORC) score, the Penn Shoulder Score (PSS), the Japanese Orthopaedic Association (JOA) score, the Simple Shoulder Value (SSV), the Korean Shoulder score (KSS) and the Rowe score.

To obtain statistically useable data, we decided to focus on the three predominantly reported scores, namely Constant, ASES and UCLA. Although these three scores have gained worldwide acceptance and seem to be used in clinical studies almost equivalently, they present differences in their evaluation strategies of the shoulder. The

three scores were therefore analyzed for the weight assigned to subjective (patient assessed) versus objective measures (physician assessed). A color code was created to distinguish the measurement method in each score parameter. The weight assigned to pain, strength, range of motion (ROM) and general functional aspects of daily life within each score were also analyzed. Each score parameter was first categorized and its weight with respect to the total score was noted. A color code was created to visualize the categories to which a score parameter belonged (Appendix Figure A 4.1). Individual score analyses including parameter color-coding is presented in Figures A 4.2-A4.4 in the Appendix. Finally, the percentages for every category and assessment method were calculated.

5 Results

5.1 Study recruitment

Thirty-one studies were included in this analysis. In 7 of them, the patient population was separately reported into individual patient groups. Thus a total of 38 patient groups contributed data to the analysis. Studies of all levels of evidence (I – IV) are represented. The majority of the analyzed studies however, are clinical series with an evidence level of IV. Most studies were performed in East Asia (14), followed by North America (10), Europe (6) and Australia (1). Figure 5.1 depicts the recruitment periods of the individual studies and their publication date. Six studies (19.4%) were published between 2006 and 2009. However, the majority of the studies (25, 80.6%) were published between 2010 and 2015.

Four studies did not report their patient recruitment periods. Of the 27 that provided this kind of information, only 5 started data collection before 2005. In 2007, the year with the highest overlap, 18 studies simultaneously collected patient data. The reporting of data recruitment periods refers to patient history and surgical data only. Bearing in mind that the clinical follow-up period generally lasted around 2 years (specified below), it becomes clear why the publication date is in average 3.7 years after the reported end of the data collection (Figure 5.1). Furthermore, with the introduction of the Double Row repair in 2003 [62] and even more the Transosseous Equivalent Repair, in 2006 [66], the number of clinical trials investigating rotator cuff repair increased continuously.

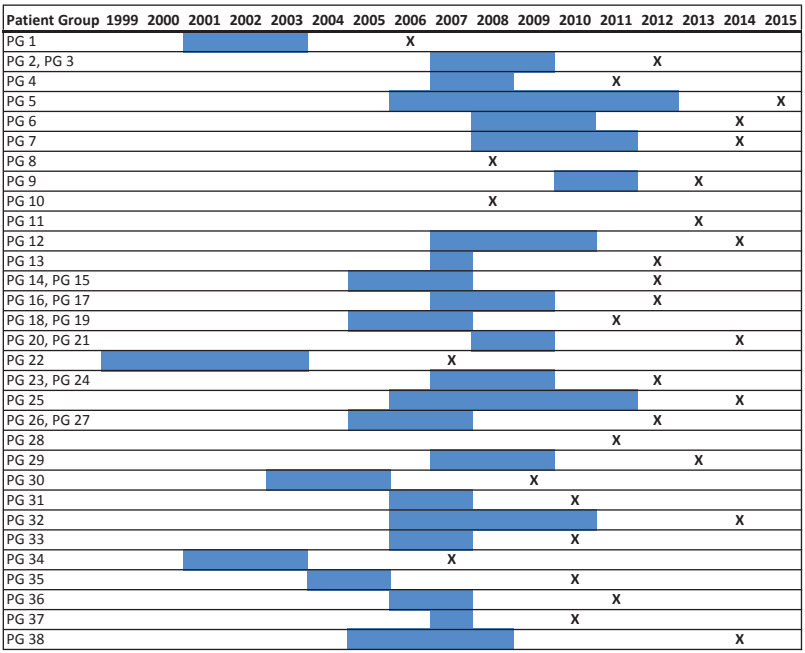

Figure 5.1: *Visualization of patient recruitment spans (blue bars) and publication year (**X**) per patient group. Assignment of the individual studies to "PG" numbers can be found in table 4.1.*

5.2 Descriptive statistics

A total of 3'611 shoulders were statistically assessed in this analysis. Mean age was reported in 35 patient groups. The overall mean age was 58.98 ± 3.83 years. Gender distribution was nearly equal; with a mean proportion of male patients at 53 ± 7%. This data further solidifies the notion that rotator cuff tears predominantly appear in older patients, without a clear gender bias. The narrow age range of recruited patients is also notable, making it difficult to link age to repair success within this data set.

Fourteen patient groups, totaling 1'398 shoulders, were treated with a "transosseus equivalent" (TOE) repair. Ten patient groups totaling 714 cuffs were repaired with a "double row" (DR) technique. The majority of patients (1499 shoulders, 9 patient groups) received a "single row" (SR) repair method. It is important to mention that two-thirds of all single row treatments came from a single study (PG25). Five patient groups (PG7, PG9, PG16, PG17, PG30) received more than one repair technique.

For 34 patient groups (2’338 shoulders) the specific suture material was directly reported or could be derived from the suture anchor type that was used. In 1’736 cases (74.3%) “FiberWire®” was used for repair. Other suture types used were “Orthocord®”, “Ethibond®”, “Ultrabraid®” and “HiFi®”. Detailed information about the large variety of used suture anchors was available from 35 patient groups (3’227 cases). In approximately half of these cases (1’587 cases), bioabsorbable suture anchors were applied. A representative example for this material type is the predominantly used “Bio-Corkscrew FT®” (Arthrex, Naples, FL, USA). Also, metal anchors such as the “G2 Anchor®” (Mitek, Raynham, MA, USA) and biostable composite materials such as the “PopLok Anchor®” (Conmed, Utica, NY, USA) were applied.

Rehabilitation data describing the onset of active assisted ROM exercise was available for 28 patient groups (2’812 shoulders). In the case of 2’338 shoulders (83%) from 21 patient groups, active assisted ROM was started 6 weeks postoperatively or later. In the remaining 17% of shoulders (7 patient groups), active assisted ROM was initiated earlier. The majority of shoulders and patient groups were therefore treated with a relatively conservative rehabilitation as it pertains to the onset of active assisted ROM. The onset of shoulder strengthening rehabilitation was reported in 31 patient groups or 2’725 shoulders, of which 2’001 shoulders (73.4%) conservatively received strengthening starting 12 weeks postoperatively. The other 26.6% were started on active strengthening earlier, before 12 weeks. 19 patient groups received a conservative strengthening protocol vs. 12 patient groups, which received an accelerated protocol starting earlier than 12 weeks postoperatively.

Patient group	Shoulders	Mean patient age	Surgery method	Imaging modality	Imaging TP (months)	Re-tear rate (%)
PG 1	52	58.3	DR	US	30	17.31
PG 2	80	55.8	SR	MRI	24	18.8
PG 3	80	55.2	DR	MRI	24	10
PG 4	87	55.4	TOE	MRI	8.5	33.33
PG 5	271	58.2	TOE	MRI	7.2	14.39
PG 6	147	62.8	TOE	MRI	23.4	17.01
PG 7	55	57.9	TOE, SR	CT	6	27.27
PG 8	39	54	SR	MRI	23	12.82
PG 9	135	73.9	DR, SR	US	12	18.52
PG 10	25	57.1	TOE	MRI	14.6	12.00
PG 11	113	58.7	TOE	MRI	multiple	16.81
PG 12	116	55.3	DR	US	12	8
PG 13	73	58.3	TOE	MRI, US	24	15.07
PG 14	25	57.46	DR	MRI, US	34.3	24
PG 15	25	58.96	TOE	MRI, US	31.7	20
PG 16	56	60.06	SR, DR, TOE	MRI, CT	12	12.5
PG 17	49	60	SR, DR, TOE	MRI, CT	12	18.3
PG 18	24	61.6	SR	MRI	27.4	16.6
PG 19	23	61.1	DR	MRI	27.6	26.1
PG 20	40	NA	SR	MRI	24	12.5
PG 21	48	NA	SR	MRI	24	8.3
PG 22	105	52	DR	CT,MRI	23	11.43
PG 23	39	56	SR	MRI, US	NA	33
PG 24	34	57.8	DR	MRI, US	NA	22
PG 25	1000	59	SR	US	6	17.40
PG 26	27	60.8	SR	MRI	33.3	22.2
PG 27	26	61.6	DR	MRI	33.5	11.5
PG 28	22	63.7	TOE	US	multiple	40.91
PG 29	107	54.8	TOE	MRI	16	10.28
PG 30	86	59.1	DR, SR	US	multiple	26.74
PG 31	78	59.2	TOE	US	multiple	8.97
PG 32	95	60.7	TOE	US	multiple	17.89
PG 33	40	61.4	TOE	MRI	16.1	17.50
PG 34	86	60.5	DR	MRI	14	17.44
PG 35	49	59	DR	US	16	48.98
PG 36	154	NA	TOE	MRI, CT	15	14.29
PG 37	45	62	TOE	MRI	12	28.89
PG 38	55	53.9	SR	MRI	28.8	36

Table 5.1: *Data overview highlighting re-tear rates, PG = Patient group (see table 4.1); Surgery method: TOE= Transosseus equivalent repair, DR= Double row repair, SR= Single row repair; Imaging modality: CT= Computer tomography, MRI=Magnet resonance imaging, US= Ultrasound; Imaging TP= Mean imaging time point for single imaging follow-up; Re-tear rate = post-operatively re-torn cuffs divided by the number of treated shoulders.*

Three imaging modalities were applied to detect re-torn cuffs. The structural integrity of 1'776 shoulders (49%) was followed with Ultrasound. The vast majority of the remaining shoulders were assessed with MR imaging. In a few cases, CT was used for structural cuff evaluation post-operatively. The mean time point of the imaging follow-up – calculated from the data of 31 patient groups – was 13.73 ± 8.25 months, with a minimum of 6 months and a maximum average of 34.3 months.

Patient group	Shoulders	Mean patient age	Treatment	Suture	Re-torn cuffs	Re-tear rate (%)	Medial failures	Medial failure rate (%)
PG 4	87	55.4	TOE	FW	29	33.33	17	58.6
PG 6	147	62.8	TOE	FW	25	17.01	20	80
PG 13	73	58.3	TOE	FW	11	15.07	3	27.3
PG 14	25	57.5	DR	FW	6	24	2	33.3
PG 15	25	59.0	TOE	FW	5	20	2	40
PG 29	107	54.8	TOE	OC	11	10.28	1	9.1
PG 32	95	60.7	TOE	FW	17	17.89	11	64.7
PG 37	45	62.0	TOE	FW	13	28.89	6	46

Table 5.2: *Data summary highlighting medial failures. PG = Patient group (see table 4.1); Treatment: TOE= Transosseus equivalent, DR= Double row; Suture: FW= FiberWire®, OC= Orthocord®; Re-torn cuffs= number of postoperatively re-torn cuffs; Re-tear rate = re-torn cuffs divided by the number of treated shoulders; Medial failures= Number of medial failures; Medial failure rate= Number of medial failures divided by all failures (re-tears).*

The overall re-tear rate was assessed in all 38 patient groups. The mean re-tear rate for 3'611 shoulders averaged at 17.76 ± 7.01 %. The lowest reported re-tear rate was 8% (PG12) the highest 49 % (PG35) (Table 5.1).

The location of the repair failure was assessed in 8 patient groups, of which 7 were treated with a TOE technique and 1 was treated with a DR repair. The mean rate for medial failures (Cho Type 2) was 49.46 ± 25.3 % with a wide spread range from 9% to 80% in certain cases (Table 5.2).

Overall pre- and postoperative results of the three major scoring systems (Constant, ASES, UCLA) and the pain VAS are visualized in table 5.3. Tables 5.4, 5.5 and 5.6 respectively show detailed, individual patient group score means for Constant, ASES and UCLA. A few studies assessed the clinical shoulder affection only postoperatively. This explained the higher sample sizes for postoperative scores. The results reflected the mean of all reported individual patient group averages recorded at the last clinical follow-up examination. The mean time point of the last clinical follow-up was 22.9 ± 6.85 months, ranging from 12 up to 37 months across patient groups.

Score System	Total Patient Groups	Total Shoulders	Mean Score	Standard Deviation
Constant pre-op	22	1811	53.57	6.7
Constant post-op	25	1996	81.61	5.42
ASES pre-op	23	1283	44.84	5.22
ASES post-op	27	1508	88.52	4.57
UCLA pre-op	13	924	15.73	3.04
UCLA post-op	16	1109	30.93	1.85
VAS pre-op	19	1527	5.91	0.82
VAS post-op	21	1632	1.21	0.54

Table 5.3: *Results of pre- and postoperative clinical scores and pain VAS. Total patient groups= Number of patient groups for which the specific score was assessed; Total shoulders= sum of all shoulders which were scored with specific score; Mean score= mean score result (calculated from the means of all data contributing patient groups); Standard deviation of the mean score results.*

Patient group	Shoulders	Mean patient age	Proportion male patients	Pre-operative Constant Score	Post-operative Constant Score	Mean last follow-up (months)	Re-tear rate (%)
PG 2	80	55.8	0.44	-	77.50	24	18.8
PG 3	80	55.2	0.41	-	78.35	24	10
PG 4	87	55.4	0.49	48	80.3	25.2	33.33
PG 5	271	58.2	0.52	63.82	85.17	27.2	14.39
PG 6	147	62.8	0.44	53.3	84.3	31.2	17.01
PG 9	135	73.9	0.46	44.4	76	12	18.52
PG 10	25	57.1	0.52	-	84.29	-	12.00
PG 11	113	58.7	0.59	61.3	93.99	12	16.81
PG 12	116	55.3	0.6	54.5	83.9	24	8
PG 13	73	58.3	0.61	52.7	74.7	30.6	15.07
PG 14	25	57.5	0.62	50.63	80.71	37	24
PG 15	25	59.0	0.54	58.73	73.96	37	20
PG 16	56	60.1	0.46	53.73	69.81	12	12.5
PG 17	49	60.0	0.37	49.93	69.83	12	18.3
PG 18	24	61.6	0.29	61.4	85.5	24	16.6
PG 19	23	61.1	0.35	63.5	85.7	24	26.1
PG 20	40	-	-	50.9	85.6	24	12.5
PG 21	48	-	-	54.2	88.7	24	8.3
PG 22	105	52.0	0.49	43.2	80.1	24	11.43
PG 23	39	56.0	0.73	55.1	85.6	24	33
PG 24	34	57.8	0.69	58.2	86.3	24	22
PG 29	107	54.8	0.61	54.5	80	16.1	10.28
PG 32	95	60.7	0.41	51.74	76.8	24	17.89
PG 36	154	-	0.54	44.44	80.47	15	14.29
PG 37	45	62.0	0.63	58	88	24	28.89

Table 5.4: *Pre- and postoperative Constant score means reported individually by patient group (see table 4.1 for patient group assignment). Additionally reported per PG: number of treated shoulders, mean patient age, proportion of male patients, and re-tear rate. Post-operative score means refer to the last clinical follow-up examination ("mean last follow-up") which is reported in months.*

Patient group	Shoulders	Mean patient age	Proportion male Patients	Pre-operative ASES Score	Post-operative ASES Score	Mean last follow-up (months)	Re-tear rate in (%)
PG 2	80	55.8	0.44	-	82.45	24	18.8
PG 3	80	55.2	0.41	-	84.20	24	10
PG 7	55	57.9	0.36	45.85	91.58	24	27.27
PG 8	39	54.0	0.62	42.23	89.43	-	12.82
PG 9	135	73.9	0.46	35.44	90	12	18.52
PG 10	25	57.1	0.52	-	93.04	-	12.00
PG 12	116	55.3	0.6	45	92.4	24	8
PG 13	73	58.3	0.61	50.4	86.2	30.6	15.07
PG 14	25	57.5	0.62	48.5	90.5	37	24
PG 15	25	59.0	0.54	58	88.46	37	20
PG 16	56	60.1	0.46	48.38	73.29	12	12.5
PG 17	49	60.0	0.37	46.27	82.9	12	18.3
PG 18	24	61.6	0.29	38.8	84.3	24	16.6
PG 19	23	61.1	0.35	38.1	84.6	24	26.1
PG 20	40	-	-	44.4	88.9	24	12.5
PG 21	48	-	-	45.8	92.1	24	8.3
PG 23	39	56.0	0.73	47.8	87.9	24	33
PG 24	34	57.8	0.69	54	89.3	24	22
PG 26	27	60.8	0.56	40.81	91.25	33.3	22.2
PG 27	26	61.6	0.54	40.8	91.38	33.5	11.5
PG 30	86	59.1	0.58	52.8	91.36	24	26.74
PG 31	78	59.2	0.63	42.1	91.9	12	8.97
PG 32	95	60.7	0.41	47.68	88.48	24	17.89
PG 33	40	61.4	0.58	-	91.22	12	17.50
PG 34	86	60.5	0.60	42.3	94.3	31	17.44
PG 35	49	59.0	0.53	45.48	82.39	29	48.98
PG 38	55	53.9	0.51	39.55	91.34	28.8	36

Table 5.5: *Pre- and postoperative ASES score means reported individually by patient group (see table 4.1 for patient group assignment). Additionally reported per PG: number of treated shoulders, mean patient age, proportion of male patients, and re-tear rate. Post-operative score means refer to the last clinical follow-up examination ("mean last follow-up") which is reported in months.*

Patient group	Shoulders	Mean patient age	Proportion male patients	Pre-operative UCLA Score	Post-operative UCLA Score	Mean last follow-up (months)	Re-tear rate (%)
PG 2	80	55.8	0.44	-	28.00	24	18.8
PG 3	80	55.2	0.41	-	28.85	24	10
PG 4	87	55.4	0.49	13.2	29.7	25.2	33.33
PG 5	271	58.2	0.52	16.59	33.24	27.2	14.39
PG 6	147	62.8	0.44	14	30.4	31.2	17.01
PG 7	55	57.9	0.36	18.28	27.4	24	27.27
PG 10	25	57.1	0.52	-	30.59	-	12.00
PG 13	73	58.3	0.61	21.6	30.9	30.6	15.07
PG 14	25	57.5	0.62	19.54	32.25	37	24
PG 15	25	59.0	0.54	21.46	30.58	37	20
PG 18	24	61.6	0.29	18	29.5	24	16.6
PG 19	23	61.1	0.35	17.7	30.1	24	26.1
PG 26	27	60.8	0.56	10.85	31.4	33.3	22.2
PG 27	26	61.6	0.54	11.38	31.53	33.5	11.5
PG 34	86	60.5	0.60	14.5	32.9	31	17.44
PG 38	55	53.9	0.51	10.01	30.94	28.8	36

Table 5.6: *Pre- and postoperative UCLA score means reported individually by patient group (see table 4.1 for patient group assignment). Additionally reported per PG: number of treated shoulders, mean patient age, proportion of male patients, and re-tear rate. Post-operative score means refer to the last clinical follow-up examination ("mean last follow-up") which is reported in months*

5.3 Results of the statistical population comparison (T-test)

Comparing the pre- and post-operative results of the Constant, ASES, UCLA Scores and the pain VAS showed significant improvement postoperatively in all systems. The highest score increase was noticed in the ASES system. The lowest raise of score points was seen in the Constant score. Figures 5.2 and 5.3 visualize the improvement of clinical symptoms achieved by rotator cuff repair. The values refer to the pre-operative status and the status at the last clinical follow-up after surgery (22.9 ± 6.85 months).

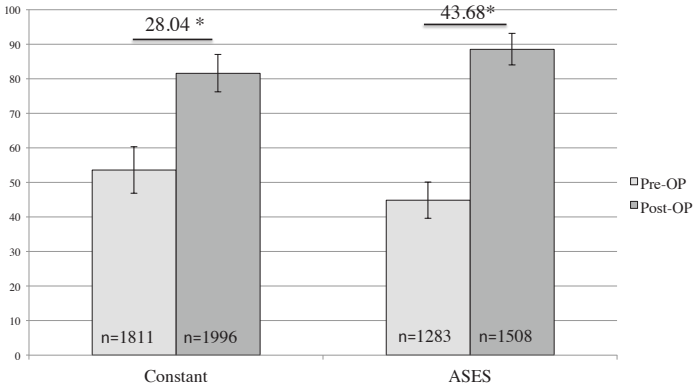

Figure 5.2: *Comparison of pre-and postoperative Constant and ASES score results, mean change indicated on black bars, * indicates P < 0.001, n is the total shoulder number, error bars show the standard deviations.*

In addition, 12 studies reported postoperative score results separately for re-torn and intact shoulders. Most of them reported only separated results of one scoring system. However, 5 studies provided data for two systems. The comparison of postoperative score results based on the structural outcome (intact vs. re-torn cuff) showed a statistical significant difference for every assessment system. Indeed, intact shoulders scored better than re-torn shoulders, as it is illustrated in Figures 5.4 and 5.5.

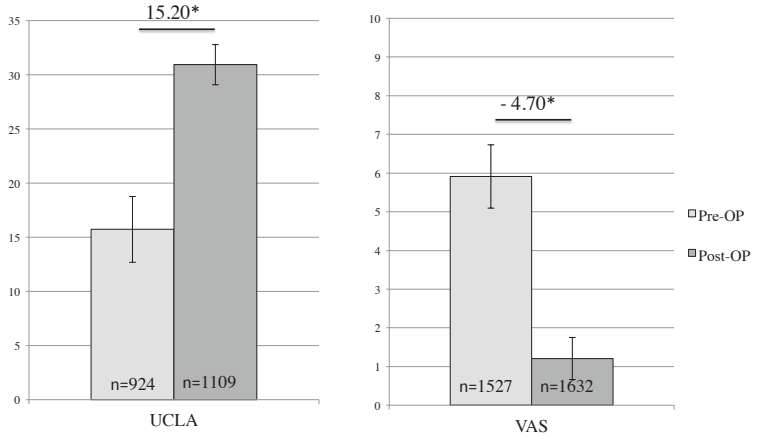

Figure 5.3: *Comparison of pre-and postoperative UCLA score and pain VAS results, mean change indicated on black bars, * indicates P < 0.001, n is the total shoulder number, error bars show the standard deviations.*

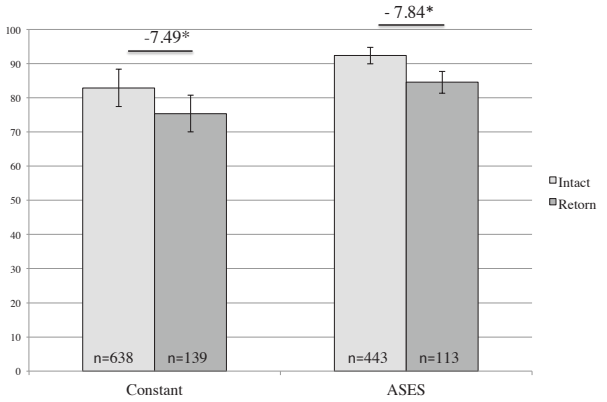

Figure 5.4: *Constant and ASES score differences between intact and re-torn cuffs after rotator cuff repair, mean difference indicated on black bars, * indicates P < 0.001, n is the total shoulder number, error bars show the standard deviations.*

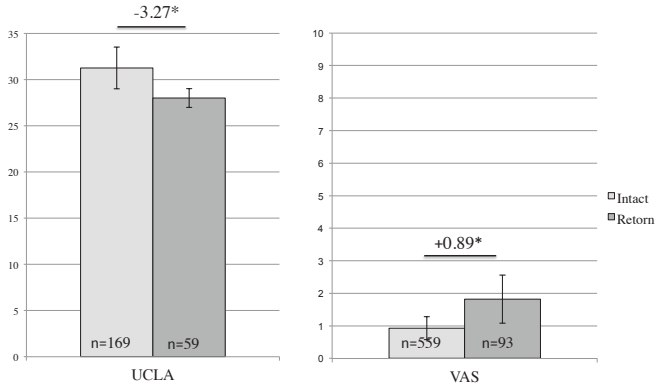

Figure 5.5: *UCLA score and pain VAS mean differences between intact and re-torn cuffs after rotator cuff repair, mean difference indicated on black bars, * indicates P< 0.001, n is the total shoulder number, error bars show the standard deviations.*

5.4 Results of meta-analysis: Random effects model predicting re-tear rate

Predictor	Estimate	P-value
Age	0.0479	<.0001
Proportion of male patients	-0.7748	0.0049
Proportion of shoulders treated with TOE	-0.1042	0.0384
Proportion of shoulders treated with SR	0.1344	0.0158
Proportion of shoulders treated with FiberWire®	-0.068	0.3305
Late onset of active ROM exercises	-0.1888	0.011
Late onset of strengthening exercises	0.2898	0.0001
Proportion of patients who received Ultrasound imaging	0.1039	0.0311

Table 5.7: *Highlighted results from the random effects model predicting re-tear rates, with estimates as well as p-values respectively indicating the effect sizes and statistical significance of each parameter included in the model.*

The meta-analysis looking at the predictors of re-tear from the parameters we collected yielded a proposed model grouping 8 parameters. Out of 38 patient groups, only 19 were included. This was due to inconsistent data reporting as only patient groups with data for all 8 parameters could be computed in the model. This generated a prediction model with 11 degrees of freedom and an Akaike Information Criterion (AIC) value of -3.89 as well as a Bayesian Information Criterion (BIC) value of -0.86, confirming the

model strength. The test of moderators gave a p value of 0.006, further solidifying the choice of these moderators. The model results are illustrated in Figure 5.6 and Table 5.7.

```
Mixed-Effects Model (k = 19; tau^2 estimator: REML)

tau^2 (estimated amount of residual heterogeneity):     0.0018 (SE = 0.0023)
tau (square root of estimated tau^2 value):             0.0424
I^2 (residual heterogeneity / unaccounted variability): 34.61%
H^2 (unaccounted variability / sampling variability):   1.53
R^2 (amount of heterogeneity accounted for):            74.43%

Test for Residual Heterogeneity:
QE(df = 10) = 14.9369, p-val = 0.1344

Test of Moderators (coefficient(s) 2,3,4,5,6,7,8,9):
QM(df = 8) = 27.5942, p-val = 0.0006

Model Results:

                  estimate      se     zval    pval    ci.lb    ci.ub
intrcpt            -2.1858  0.6130  -3.5660  0.0004  -3.3872  -0.9844  ***
age                 0.0479  0.0108   4.4187  <.0001   0.0267   0.0692  ***
propmale           -0.7748  0.2752  -2.8154  0.0049  -1.3142  -0.2354   **
toe                -0.1042  0.0504  -2.0702  0.0384  -0.2029  -0.0056    *
sr                  0.1344  0.0557   2.4145  0.0158   0.0253   0.2435    *
fw                 -0.0680  0.0699  -0.9732  0.3305  -0.2050   0.0690
as.factor(acat)1   -0.1888  0.0742  -2.5435  0.0110  -0.3342  -0.0433    *
as.factor(scat)1    0.2898  0.0756   3.8326  0.0001   0.1416   0.4380  ***
us                  0.1039  0.0482   2.1554  0.0311   0.0094   0.1984    *

---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

> AIC(res3)
[1] -3.891652
> BIC(res3)
[1] -0.8658008
```

Figure 5.6: *Results snapshot of the generated script describing the mixed model with all included parameters, test of moderators, significance, estimate values, AIC and BIC values. Parameters included are "age", "propmale" (proportion of male patients), "toe" (proportion of shoulders treated with TOE), "sr" (proportion of shoulders treated with SR), "fw" (proportion of patients treated with Fiberwire®), "as.factor(acat)1" (late onset of active ROM exercises), "as.factor(scat)1" (late onset of strengthening exercises) and "us" (proportion of patients who received Ultrasound imaging).*

In short, higher age was associated with higher re-tear rates and studies with a higher proportion of females were also associated with higher re-tear rates. Regarding therapy parameters, patient groups treated with TOE were associated with lower re-tear rates while those treated with SR were associated with higher re-tear rates. As for rehabilitation protocols, the early onset of active ROM exercises and the late onset of strengthening exercises were associated with a higher re-tear rate. Finally, the use of ultrasound versus other imaging modalities (MRI, CT) was also associated with higher

re-tear rates. The use of FiberWire® however, while included in the model, was not significantly associated with re-tear rates but could not be omitted as a parameter, possibly because of its interaction with other parameters within the model. We attempted to investigate this interaction and found it likely to be a mathematical artifact rather than a true clinically relevant interaction but further testing is required at this stage.

5.5 Results of meta-analysis: Random effects model predicting clinical scores

A random effects model was also performed looking at predictors of clinical scores (Constant, ASES, UCLA or VAS). It was not possible to produce a strong model grouping predictors consistently, mainly due to reporting gaps and a relatively high AIC.

5.6 Results of the clinical score analysis

Figure 5.7 shows the distribution of the assessment method (Physician vs. Patient Assessed) per score. The UCLA score consists of approximately 2/3 patient-assessed measures and 1/3 physician assessed components. In the Constant score, only one-fourth is patient-based and in the ASES subjective measures alone account for the whole score.

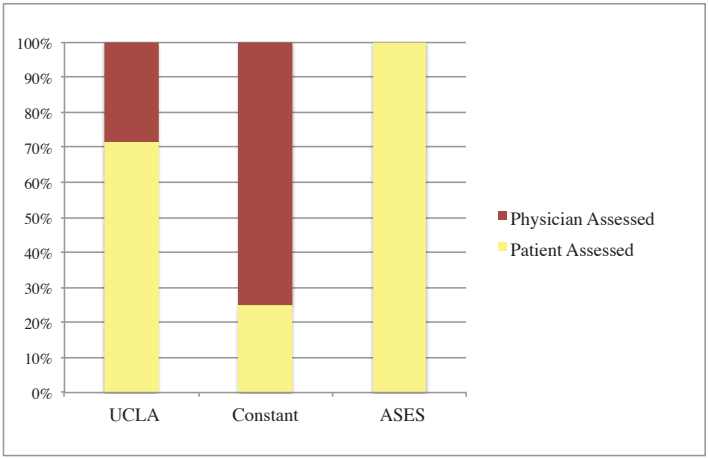

Figure 5.7: *Proportion of Physician assessed vs. Patient assessed parameters in clinical scoring systems*

While physician assessed measures are often regarded as objective, it may not always be the case. Indeed, an example for this is strength testing in the UCLA score in which strength is rated by the examiner as good or poor (with gradual stages in between). This assessment would not produce a quantitative measure of strength, but it allows evaluating strength in relation to patient age, gender and general condition. However, in the Constant score, all parameters that are physician assessed are measured on objective scales. In fact, the subjective components only account for 25% of the final score. Thus it can be said that the Constant score, although not adjusted for age and gender, leads to a very objective evaluation of shoulder function.

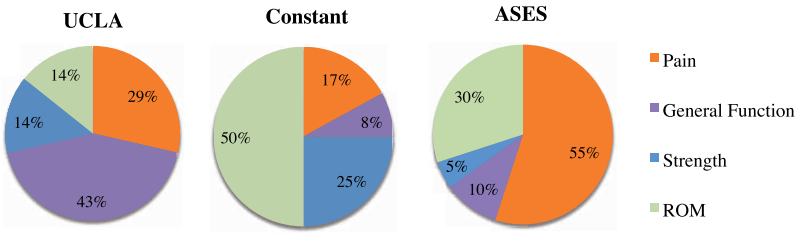

Figure 5.8: *Clinical grading systems UCLA, Constant and ASES, compared side by side for their proportionate focus on pain assessment, general function assessment, strength or range of motion (ROM) assessment.*

As seen in figure 5.8, there were great differences detected between scoring systems regarding component category weights. For instance, in the ASES score, the visual analog scale for pain accounts for 50% of the total score, whereas in the UCLA score, the pain parameter impacts 28.6% of the final result and in the Constant score it only accounts for 17% (see also Appendix).

6 Discussion

In this work the crucial components of temporary rotator cuff repair were identified (Figure 3.6). Potential failure mechanisms of these components were presented and analyzed in a comprehensive literature review. Finally, data from 3'611 surgical cases was compiled and thoroughly analyzed in order to detect the most relevant mechanism of failure after rotator cuff repair and to identify important predictors of structural and functional outcomes.

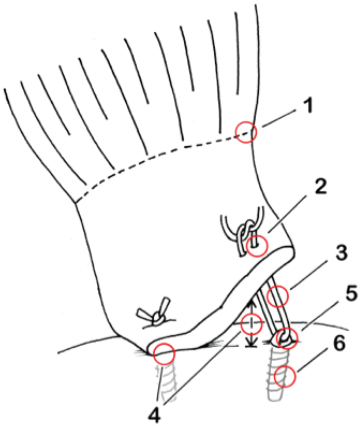

Fig 3.6 *recalls the repair components that are potential failure foci at the same time.*

6.1 Predominant locations of failure

One of the goals in this work was to identify the predominant modes of failure in the clinical set-up. The major problem in the identification of failure mechanism based on clinical imaging data is that it can identify and possibly locate a recurrent defect but it cannot assess the underlying cause. The only failure mechanism that is individually assessable is the medial tendon failure. A total of 7 studies looked for the location of failure in 8 treatment groups (see table 5.2). Seven groups were treated with a suture bridge repair technique, one with a conventional double row method. In average every second re-tear was located medially. However, the range from 9 % (PG29) up to 80 % (PG6) medial failure rate highlights the variability of this occurrence. In these two extremes, patient baselines differed. In PG29 fatty infiltration grades above Goutallier II

and retraction grade Patte III were excluded. Thus, it is likely that there were no massive tears present in this patient group. However PG6 included all Goutallier grades of fatty infiltration and also massive tears. Furthermore the mean patient age in PG6 was 62.8 whereas it was only 54.8 in PG29. These baseline differences might partly explain the contrasting medial failure rates and also the differing overall re-tear rates. Worse baselines correlate with worse tendon condition and thus with a higher tendon vulnerability. Nonetheless equally important are differences in surgical techniques. Neyton et al. (PG29) emphasize the importance of moderate suture bridge tensioning, as they believe there is a threshold in between beneficial and harmful tendon compression [75]. They explained their low medial failure rate with several technical details: Besides using only one suture per anchor, they only applied 2 anchors at the medial row in order to avoid potential suture related tendon necrosis with too many sutures. Furthermore they left a security margin to the musculotendinous junction of at least 5mm and performed manual suture tensioning instead of using a tensioning device. Choi et al. did not report precautious surgical details [45]. Another interesting finding to note in that context is that Neyton et al. were the only study of the 8 mentioned above to use another suture material than “FiberWire®”. They used “Orthocord®” which was found to have lesser abrasive properties [89, 90]. Thus, suture material properties are also important to consider in the context of medial cuff failures.

From these findings, it still remains unclear what mechanism predominantly leads to the occurrence of medial tendon failures after rotator cuff repair. However, it seems that repair technique, especially careful suture tensioning and the avoidance of too many sutures passing the tendon, can maintain tendon tissue health and therefore improve healing and lower the risk of medial re-tearing.

Regarding tendon-suture interface related failures, very little information was detectable. Miller et al. reported frequent ultrasonographic appearance of suture material in the visualized tendon gap [123]. Thus they believed failures at the suture-tendon interface to be the predominant mechanism of re-tear. As mentioned earlier, Cummins et al., having the opportunity to evaluate failure mechanisms directly at revision arthroscopy, found 19 of 22 re-tears to have failed at the suture tendon interface [88]. These findings strongly suggest, that the suture-tendon interface is a critical component of the repair.

No hints could be found on the extent of purely suture related failures within the clinical studies. However, it seems that suture slack and knot-security play a minor role in the picture of RCR failures and are likely indirectly taken into account when evaluating gap formation.

Any re-current defect that is not retraceable to a medial failure can be seen as a failure at the tendon-bone interface. Again, disintegration of this repair component is often a result of failures at other repair components. It can however also reflect biologic healing failure, as the rare appearance of late re-tears (after six months) suggest. In these cases the repair construct survived all stages of post-operative rehabilitation. Why the tendon finally still fails to heal remains unclear. Explanations for this might be inferior bone and/or tendon condition or systemic concomitant diseases related with decreased healing potential like diabetes mellitus [98].

There was no indication for failures at the anchor-suture interface. But again, this failure location is not assessable within the normal clinical set-up. Failures at the anchor eyelets of conventional anchors are unlikely to reflect a relevant problem today. However, as explained above, suture slippage in knotless anchors might be a considerable mechanism of failure with only little possibility of direct assessment.

Only 3 cases of anchor related failures were reported within the analyzed studies. Deutsch et al. reported an intraoperative anchor pullout that could be corrected with a larger diameter anchor [77]. Neyton et al. reported two cases of anchor breakage that required revision [75]. With 2 material failures and only 1 anchor-bone interface failure (that could be fixed intra-operatively), this component of the repair seems to be solid and does not represent a relevant location of failure in current concepts.

6.2 Re-tearing as central problem in rotator cuff repair

6.2.1 Detected average re-tear rate

As re-tearing of repaired rotator cuffs remains an unresolved challenge, its extent is commonly applied to judge the success of the procedure. Although not every analyzed study provided clinical outcome assessment, all of them assessed the structural outcome and reported a re-tear rate for their patient groups. Combining the reported rates of 38 patient populations (3’611 shoulders), we detected a weighted mean re-tear rate of 17,76% assessed at a mean time point of 13.7 months. This figure is lower compared with the mean rate of 26.6% (23.7 months after repair) found in a recently published

systematic review on over 8'000 shoulders[57]. This may have several reasons: The inclusion time span in McElvany et al. ranged from 1980 to 2012 while we defined it to be from 2005 to 2015. Although RCR research is an old field, the picture in the 1980s was a different one than in the late 90s and yet again in 2015. A lot of knowledge has been amassed within this time and the evolution from open to all arthroscopic procedures took place. Thus it can be assumed, that the inclusion of earlier publications may lead to a higher mean re-tear rate. The character of the two reviews is also different, with McElvany conducting a systematic literature search while our work included studies following strict criteria but our listing was not meant to be exhaustive.

However, independent of the mean value, the range in re-tear rates in our study spanned from 8% (PG12) up to 49 % (PG35), impressively showing the existing differences. A little less than 1 re-tear for every 10 repaired cuffs is an acceptable result considering the challenges of RCR. However, a 50 % re-tear rate clearly reflects an inacceptable outcome.

Two questions therefore arise, when the success or downfall of RCR is judged by re-tear rates: (1) Are the detected rates true? and (2) is the rate of structural failure a suitable measure to evaluate the effectiveness of RCR?

6.2.2 Accuracy of detected re-tear rate

In clinical settings, re-tears can only be detected with help of medical imaging. Three modalities have been used and validated. These are MRI, Ultrasound and CT imaging. Although it was found that CT-Arthrography and MR-Arthrography show similar diagnostic performance on the evaluation of rotator cuff tears [134], within the analyzed studies, only 4 included CT-A to assess postoperative cuff integrity. Although slightly more cost efficient, due to radiation exposure CT or CT-A assessment is not the imaging method of choice after rotator cuff repair. Approximately an equal number of shoulders were followed-up with MRI and US. It was shown that these modalities provide comparable sensitivity and specificity in the detection of rotator cuff tears and can equally be applied [135-137]. The two modalities can also equally be applied for the assessment of postoperative cuff integrity [138]. However, for this purpose a slightly lower sensitivity of ultrasound assessment was found compared with MRI results [139]. Intra- and inter-observer agreements are very good for both modalities [138, 139]. However, and especially for Ultrasound assessment, the experience of the operator

plays a major role [140]. Considering the availability of Ultrasound and its associated patient convenience, it presents a good alternative to MRI scans in order to evaluate the post-operative integrity. Due to Ultrasound's lower resolution, however, it would be expected that the detected re-tear rate might be slightly underestimated. On the other hand, only 10% of re-attached tendons show a normal signal in MRI. Artifacts produced by metal anchors, fluid leakage in the subacromial space due to arthroscopic portals and also by the physiologic inflammation process are frequently seen and can make the interpretation of postoperative MRI difficult at early follow-up [139]. It is interesting to note that our re-tear rate prediction model showed the opposite trend, namely that the studies using Ultrasound seemed to report higher re-tear rates. Although far from a conclusive causality, it points to an interesting trend, perhaps indicating that the operator's judgment, in these cases, can outweigh the inherent over or under estimation of objective re-tear detection by MRI or Ultrasound.

Indeed, the time point of imaging follow-up is also important to consider as it may influence the re-tear rate independent of modality related limitations. Only few studies assessed the timing of cuff re-tears. While most of them found re-tears to occur predominantly within the early postoperative period (before 6 months) [74, 123, 125, 141], a recent publication detected the majority of re-tears between 12 and 24 months [142].

Early re-tears suggest mechanical failure, whereas later re-tears rather suggest a healing failure [51]. Miller et al. looked specifically at large and massive rotator cuff tears. Of 22 patients, 9 were subject to re-tearing. 7 of the 9 re-tears occurred before 3 months. Only 2 re-tears occurred within the immobilization phase, the majority occurred when passive ROM exercises and later active ROM were performed [123]. This finding suggests re-tearing to be mainly a biomechanical phenomenon and puts focus on the potential influence of shoulder rehabilitation protocols. Iannotti et al. presented similar results. They found 42% of the re-tears to occur within 3 months and 53% between 3 and 6 months [74]. Again there was only one re-tear within the immobilization phase, and the vast majority within the active assisted ROM and gradual strengthening phases. This emphasizes the relation of load bearing and re-tearing. That in Miller's investigation re-tears occurred mainly earlier than in Iannotti's might be explained by the fact that Miller treated only large and massive tears whereas Iannotti had a medium tear size average. Structurally successful repair of massive tears is limited as shown by

Galatz et al. [143]. It is likely that it requires less strength to re-tear a repaired massive defect than an originally smaller lesion.

Although with wider imaging intervals, Koh et al. [141] and Park et al. [125] could confirm the findings of Miller and Ianotti. Park detected 67% of the re-tears to occur before 4.5 months and Koh found that the number of re-torn cuffs detected at 6 months remained consistent at 19 months. Interestingly, Nho et al. [124] found 7 of the 30 re-torn cuffs that they detected 12 months postoperatively, to be healed at 24 months. Conversely, Stahnke et al. found 5 of the 6 re-torn cuffs in their serial imaging trial to have occurred between 12 and 24 months [142]. This finding is interesting as it suggests very late failures to be predominant. However, their sample size was very small (n=13) compared to other studies. Summarizing and weighing the findings, the vast majority of re-tears seem to occur before 6 months. A few outliers have been detected mainly between 6 months and 1 year. Thus an imaging time point around 12 months seems to best reflect the actual re-tear rate. Considering the finding of Nho et al. a later time point is potentially correlated with lower rates. However, the secondary healing of re-torn cuffs blurs the picture of actual re-tear rates after surgery and it is unlikely that late secondary healing of a re-torn cuff will provide similar tissue properties as direct primary healed tendons.

Our meta-analysis further emphasized the importance of load bearing on re-tearing during rehabilitation. Indeed, the model we developed associated a later onset of active ROM exercises and an early onset of strengthening exercises to a lower re-tear rate. Here again, while the model does not prove causality, it is conceivable that, in order to achieve lower re-tear rates, active ROM exercises must be delayed for the preliminary healing tissue to set while strengthening exercises must start earlier than 12 weeks postoperatively in order to avoid tissue fibrosis or stiffening and to allow for the new tissue to benefit from mechanical stimulation during regeneration. This of course must be proven in a prospective study looking specifically at these effects but the theory behind such a mixed rehabilitation regimen is valid, with both a conservative onset of active ROM and an accelerated onset of strengthening.

6.2.3 Re-tear rate a suitable measure to judge surgical success?

It seems logical that a re-torn cuff will clinically affect a shoulder like an originally torn cuff. However, it was found that patients regardless of a recurrent defect significantly benefit from the surgery in terms of pain relief and functional improvement [44-47]. In fact, multiple studies did not detect significant clinical differences in between re-torn and intact cuffs postoperatively [48-51].

Conversely, other studies were able to detect statistical evidence for structurally intact cuffs to show favorable clinical outcomes when compared to re-torn tendons [36, 75, 76, 124]. Abduction strength was especially found to be significantly lower in the presence of a cuff re-tear [46, 74, 124, 126]. Similarly, in their systematic review with the purpose of detecting clinical difference of radiographically healed and re-torn rotator cuffs, Slaubaugh et al. found a trend towards a clinically superior outcome for healed cuffs [144].

In our work, the comparison of the available postoperative clinical score data (Figures 5.4 and 5.5) showed significantly lower scores for re-torn cuffs in all 3 grading systems (Constant, ASES, UCLA) and higher values on the pain VAS. This finding shows clinical impact of recurrent cuff defects.

It is evident both from our analysis of the literature and our statistical work that recurrent defects after RCR have a notable clinical impact. However, the presence of structural failure is not equivalent with a clinical failure. Compared to their baseline condition, the majority of patients with a cuff re-tear still significantly benefit from surgery. It is important to assess and report re-tear rates but at the same time the assessment of functionality and pain level is inevitable in order to best evaluate the surgical success of RCR. This is where a thorough reporting of clinical grading for patients with an intact or a re-torn cuff as well as their baseline pre-operative scores is important in order to determine the link between structural and clinical findings.

6.3 The differences in clinical scoring systems and their relevance

Grading systems are widely used in medicine in order to assess disease severity, compare clinical data and measure treatment efficacy. In orthopedic shoulder surgery several scores have been developed to evaluate clinical outcomes. However, not all scores are equivalently applicable to shoulder related symptoms. Indeed, the validity and reliability of scores vary with different diseases of the shoulder [145]. To assess

rotator cuff specific symptoms many scoring systems have gained wide acceptance and are frequently utilized for clinical assessment.

Although their assessment strategies and component weights differ greatly (as depicted in figure 5.7 and 5.8) all of the 3 majorly applied scoring systems – namely Constant, ASES and UCLA score scales – revealed a significant difference ($P<0.001$) in between re-torn and intact cuffs. It is most likely that studies that cannot find significant differences but a strong trend in favor of the intact cuff group are underpowered. Due to the lack of statistical useful baseline data, it was not possible to thoroughly analyze the correlation of preoperative structural cuff condition and clinical baseline score. However, it seems that the inclusion of massive tears and high grades of fatty infiltration and tendon retraction do not generally correlate with lower mean baseline scores (PG6, PG22).

Looking at the overall score values shows, there are differences in the mean baseline values. The ASES and UCLA systems show lower mean baseline values than the Constant score (see table 5.3). The improvement in both scores after surgery however is significantly greater than in the Constant system (see figure 5.2 and 5.3). This is most likely explained with the category weights. While in the Constant score pain and general function only account for 25%, in the UCLA and ASES those 2 categories impact 72% and 65% respectively. Thus, the higher improvement percentages in the ASES (97.4% in relation to baseline) and UCLA (96.6%) score suggest pain relief and with it general function improvement to be more effective (or faster) than the regain of strength and ROM. In fact, the ASES score shows the highest improvement, indicating pain relief to be the most important postoperative effect, although the difference between ASES and UCLA scores is marginal.

Not only the different weighing strategies but also mean patient age and gender influence the lower increase of the Constant score (52.3%). This system measures strength in pounds (lbs.) that can be lifted to shoulder level at 90° abduction in the scapular plane. Lateral abduction strength of 107 N (24 lbs.) is evaluated with the full 25 points for this score category. Thomas et al. found in their examination of the Constant score that less than 50% of the men of a mid-age, symptom-free test population and no women were actually able to perform this [146]. In other words, the vast majority of people will not reach the total value in the Constant score despite having a healthy shoulder. The difference between a pain-free and fully mobile shoulder

in a 75 year old female and a 35 old male for example could easily be as much as 15 points. Conversely, in the UCLA and ASES scores, where strength is rated by the subjective impression of the physician (UCLA) or with a subjective question (ASES), a healthy shoulder is most likely to score the full points. Interestingly, despite these differences, the Constant score was still sensitive enough to distinguish re-torn from intact cuffs. This might be related to the fact that abduction strength was found to be generally lower in patients with a re-tear.

The analyses of the scores' assessment ratio, physician vs. patient (Figure 5.7) showed impressive differences. Whereas in UCLA one third is physician based, in the Constant score it is approximately 75 %. In fact, the rated and thus result determining part of the ASES system is fully patient self-administered. It starts with a section of six questions. Two of these aim to get a picture of the individual amount of shoulder use and four investigate for pain level. However, answers in this section are not rated and thus do not influence the result. The second part is composed of a 10-point visual analog scale for pain and 10 questions that are tied to 4 Likert- scale- type answer options each. All of these questions are highly subjective measures. They aim to investigate ROM, strength, pain and general function. As patients might differ greatly in their perception of pain, their ideas of "how difficult it is for them to put on a coat" (see ASES question 8, Figure A 4.4) vary as well. For example, taking two patients with equally limited ROM scoring this task as "somewhat difficult" or "very difficult" leads to a difference of 1.33 points in the final result. Thus, one would assume that the ASES score would show the highest variations. Very interestingly, the mean ASES baseline score and also the mean post-operative value, have the lowest standard deviations compared to other scores. This again, identifies pain to the most important factor in rotator cuff tears and its relief to be the greatest effect of the surgery. This explains also the general finding that patients with a structural repair failure still significantly benefit from the intervention. Concomitant procedures like debridement, acromioplasty, biceps tenodesis or tenotomy and tendon mobilization are not only important precursors for successful cuff refixation, but at the same time eliminate consistent noxe and thus effectively reduce pain regardless of the primary goal of tendon repair.

When assessing clinical, respectively functional shoulder status, the objective/subjective measure ratio and as well the category weights of a scoring system have to be taken into

consideration. Especially when comparing score results, the nature of a scoring system should be well known and understood.

6.4 Methodological considerations

The analyzed data was collected from a total of 31 publications. Descriptive statistical analyses and a meta-analysis of the data were performed. Due to a lack of reporting standards in many publications and despite the large amount of data points, performing a meta-analysis was particularly challenging (Appendix Figure A 6.1 visualizes reporting incidences for all assessed parameter). One challenge there was the loss of patients for follow-up examinations. This means that clinical and imaging outcome data was not available for a portion of the originally recruited patient population with several studies reporting recruitment and outcome data for different sample sizes (Cho2011 et al. [36], Kim KC et al. [50], Voigt et al. [128]). This was especially critical when comparing the preoperative and postoperative functional scores with non-matching sample sizes. To counter that limitation, we had to assume that parameters means describing the larger data set in each individual patient group also represented the smaller follow-up data set after patient dropped out. While it is important to report on as much data describing a population as possible, investigators should aim to report complete data sets with a consistent sample size and, when that is not possible, report population data from the patients who were followed throughout. Indeed, when analyzing results of published clinical trials, drawing correlations between recruitment criteria, therapies used and clinical outcome is only possible if these three data sets are reported with continuity.

A similar problem was the use of more than one therapy method in a patient population without specific sub-population description. As many studies are retrospective, depending on the main purpose, different repair methods are reported in one study without clarifying which patient received which treatment (i.e.PG9). In these cases it must be assumed that the therapies produce equivalent outcomes, independent of patient related factors. However, it has been shown that there are technique dependent differences in re-tear rates [147]. While the aim of a specific clinical report may not particularly be the comparison of surgical therapies, here again the consistent and transparent reporting of sub-population distributions is crucial (i.e. how many patients within a treatment group in a study comparing rehabilitation protocols received suture bridge or double row repair). This trend of under-reporting, beyond the realistic

limitations of clinical trials (patient drop out sometimes cannot be avoided), was widely present in the studies we analyzed, going beyond a few outliers. This effect can seriously undermine the impact of reported clinical data.

Another methodological challenge we encountered, is in the reporting of outcome parameters. The two major outcome measures after rotator cuff repair are (1) the structural outcome and (2) the functional (clinical) outcome. Their mutual dependence has been discussed and is still of major interest in the current literature. However, many studies still do not report their clinical findings separately per structural outcome group, meaning separately for patients with re-torn vs. patients with intact tendons (PG8, PG25, PG35). Instead they provide overall outcome means. This strategy may show the effectiveness of RCR, but it does not allow the evaluation of the link between structural and clinical outcomes. In order to further investigate the clinical influence of structural failure, studies should not only aim to report postoperative clinical data per structural outcome groups but also to provide preoperative clinical data separately. This will allow the evaluation of the relationship between preoperative functional shoulder affection and re-tear risk, answering an important question in RCR.

Regarding patient inclusion and recruitment criteria, we had to counter the challenges faced here by omitting certain parameter from our statistical analysis, even though they were powerful descriptors of the patient population baseline. Indeed, while most studies provided inclusion and exclusion criteria for their patient recruitment, there was no agreement on the reporting of these criteria. In general, baseline data can be split in patient-related and disease-related factors. Age, gender and concomitant diseases would be patient-related and tear size, grade of fatty degeneration and tendon retraction directly disease-related factors. For instance, older age, greater tear size, higher-grade fatty infiltration and further tendon retraction have been found to increase the risk of a cuff re-tear [36, 45, 77, 126, 148]. These parameters are therefore very effective tools to distinguish the initial affection severity of a patient population and later allow the evaluation and validation of outcome differences. Thus, any treatment-influenced outcomes might be shielded by baseline differences between studies, causing outcome differences to be misinterpreted as treatment dependent. The reporting of baseline data differed tremendously within the analyzed studies. While several studies provided detailed baseline analysis for their study populations (PG4, PG6, PG11, PG31), others reported averages (PG18/19, PG23/24, PG16/17 and yet others only inclusion limits

(PG29, PG9) or even no baseline data at all (PG10). This reporting diversity in combination with a lot of missing data made it impossible to statistically exploit any baseline parameter besides patient age, gender and pre-operative clinical scores. Indeed, the lack of statistical baseline consideration is a limitation of this meta-analysis and would be of great help in order to conduct full cross sectional analyses in the future.

6.5 Conclusion

This literature review showed that rotator cuff repair significantly reduces cuff tear associated shoulder symptoms, despite a high rate of structural repair failure. Although patients that suffer a post-operative cuff re-tear still experience a significant improvement of clinical symptoms after surgery, structurally intact repairs generally present higher clinical scores indicating intact tendons to be associated with better shoulder function and lower pain level.

Rotator cuff re-tearing is a multifactorial occurrence and many different mechanisms can lead to failure of the individual repair components. The inconsistent rates of medial failures associated with modern techniques indicate that temporary repair concepts have reached a level of biomechanical strength that can also be detrimental to tendon healing instead of exclusively beneficial. For future technique innovations, it must be recalled that the repair can only be as strong as its weakest link. Thus, further research for repair improvement needs to consider the tendon as the weak link and identify strategies to combine high repair strength with tissue compatibility.

Although, there is a massive body of literature in the field of RCR and the publications per year have progressively increased, there is a lack of reporting standards. In order to translate the amassed knowledge into evidence that may help to further understand rotator cuff pathology and improve the treatment options, agreements on data reporting standards and clinical study design are needed.

7 Perspective

7.1 General remarks

Despite a tremendous technical evolution and progressively increasing knowledge amassed by numerous clinical trials investigating the challenges of rotator cuff repair, re-tearing of repaired cuff tendons remains to be a frequent phenomenon after RCR. It seems that we are at a point where simply comparing surgical methods and measuring patient benefit cannot provide additional information to significantly improve the structural outcome after repair. In order to further decrease re-tear rates and simultaneously increase the clinical efficacy of surgery in the future, it will be necessary to address the "hot spots" of rotator cuff repair with focused research. Much more effort needs to be invested in understanding the many failure mechanisms as well as identifying strategies to avoid failure. Biomechanical cadaver studies can provide useful data in this process, however real evidence can only come from in vivo studies as these allow the investigator to consider the effects of the dynamic healing process. However, the potential of in vivo studies in terms of human clinical trials is limited, as many currently asked questions would require direct repair site assessment. Of course "follow-up arthroscopy" is not an option and repair site assessment is limited by conventional imaging methods. Well-designed animal models may help to bridge the gap between the limitations of cadaver studies and those of clinical trials.

As the failure mechanism analysis revealed, the tendon-bone interface is the most vulnerable repair component as many of the described mechanisms may induce gap formation and a subsequent loss of contact. Thus the limitation of repair site gap formation seems to be a promising approach towards further outcome improvement.

In the following, an animal model is presented that was specifically designed to investigate postoperative gap formation between the repaired rotator cuff tendon and its bony footprint. Additionally, the model allows assessment of other aspects like general tendon to bone healing questions and implanted biomaterial efficiency and biocompatibility.

7.2 Ovine rotator cuff repair model

7.2.1 The sheep shoulder as animal model for rotator cuff repair

Although a sheep's shoulder anatomy is not directly comparable to the human, ovine models are well established and accepted in rotator cuff research [149-152]. The ovine infraspinatus tendon has a similar size and thickness as the human supraspinatus tendon. With 60-90 kg, adult sheep also have comparable bodyweights. As quadrupeds per se have different load bearing on the rotator cuff tendons, both in amplitude and direction, it is obvious that the forces acting on ovine and human cuff tendons differ. However, since muscle and tendon size and also bodyweight are very similar, the sheep is a suitable model animal to test new repair methods, examine potential failure mechanisms and investigate musculotendinous changes induced by rotator cuff tears.

7.2.2 The procedure

After a lateral approach to the right shoulder, the caudal half of the infraspinatus tendon is cut close to its humeral insertion. It is important to cut perpendicular to the tendon surface in order to create an equally edged gap. If the tendon were released right at the insertion, the tendon stump would have more of a triangular than rectangular shape, as it inserts flat and oval into the greater tubercle. If the incision is performed correctly, a small triangular tendon remnant will stay attached to the footprint and may be excised by cutting it right at the bone.

After drilling four bone tunnels, two deep and two superficial from the tendons' caudal footprint region towards the bicipital groove, two sutures are placed in the tendon. One is positioned right above the cranial incision end, the other grasping the caudal tendon edge (Figure 7.1). After suture placement, a release incision is set proximal to the sutures close to the musculotendinous junction. It includes again the caudal half of the tendon. Its purpose is to modulate mechanical strain postoperatively to protect the repair from excessive loading.

The suture threads (two cranial, two caudal, one deep, one superficial each) are then brought through the corresponding drill tunnels and fixated laterally by knotting corresponding threads over an 8-hole button plate, which is placed directly onto the humerus in the bicipital grove. The strain on the sutures will determine the gap width in between the tendon edge and the bone. That means the gap size can be adjusted to the desired distance by modulating the knotting strength.

Within the caudal tendon suture row runs a black 2/0 Supramide® suture (Figure 7.1). It is guided through the caudal superficial bone tunnel and cut at a defined length of 20mm. As this thread bridges the gap, a change in length of its distal end will indicate a change in gap size.

Furthermore a steel wire is placed with a simple stitch in the caudal tendon proximal to the gap. A small screw is finally drilled into the caudal aspect of the greater tubercle, approximately 5mm caudodistal to the caudal tendon insertion. The distance between the steel wire and the screw is accurately measured with a caliper. Again, a later change in this distance will indicate a change in gap size. With regard to the radiopaque properties of the markers, the distance can as well be measured from a radiograph.

A detailed step-by-step surgical protocol with images can be found in the Appendix.

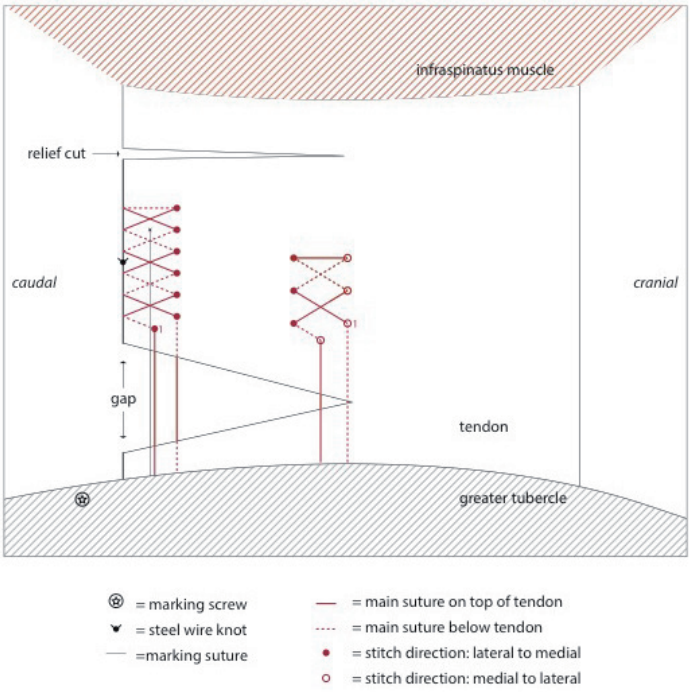

Figure 7.1 *(© Helen Kindt): Schematic presentation of stitching pattern and marker position, lateral fixation of sutures are not depicted.*

7.2.3 Post-operative treatment and care

It is necessary to provide sufficient postoperative analgesia (e.g. Buprenorphine on the day of surgery, Carprofen until 5 days post-OP) and prophylactic antibiotic coverage (e.g. Penicillin and Gentamycin for 5 days). This regimen has proven to work reliably in sheep undergoing an operation with a comparable severity.

Although the release cut is thought to take most weight from the repair site, contraction of the infraspinatus muscle, which is a lateral stabilizer and flexor of the ovine shoulder, will still produce strain on the repaired tendon. To prevent an early rupture, the sheep are positioned in a large animal suspension system immediately after surgery.

Figure 7.2: *Sheep in suspension system to prevent excessive load bearing on operated shoulder.*

This hammock-type construct restricts the animals' motion radius and prohibits them from lying on the ground. Therefore it reduces the amount of load on the repaired tendon which is high when the sheep stand-up after lying on the ground. The animals can stand without restriction and also turn and walk a few steps to their hay manger and water. During the suspension phase the animals are housed separately with visual contact to each other. After 2 weeks they are taken out of the suspension system. From

then on, the sheep can be housed in pairs. They are allowed to ambulate freely within a limited amount of space (approx. 3-4 sqm per animal) to prevent them from excessive motion like running and jumping.

7.3 Model outcome analysis

The model was originally designed to assess and evaluate the effect of repair site gap formation. However, it also allows investigating a wider field: It can provide information about the biocompatibility and performance of new suture materials and it can help to further understand the challenges and timing of tendon-to-bone healing.

Concerning gap formation, the model mainly allows assessment of two questions: What is the critical gap size that will impede the healing process? How does the gap size change postoperatively?

7.3.1 In-vivo analysis

After surgery the animals need to be observed at least twice daily. Signs of severe lameness and external findings, like excessive swelling or wound healing complications may indicate repair failure or wound infection. The only in-vivo assessment that can be performed with this model is radiographic tracking of gap formation. Radiographs are shot in a mediolateral direction, 90° to the scapular plane. By taking serial radiographs, the difference in the distance between the radiopaque markers (steel suture and marking screw) will provide information about the gap size over time. In order to achieve exact measures, the serial radiographs need to be taken in the exact same plane. Sedation of the animals is required for this purpose.

7.3.2 Ex-vivo analysis

Except the serial imaging, all other assessments methods per se require the death of the animals. As it is not permitted to bring products of research animals into the human food chain, it should be aimed to still use as much as possible of the animals after harvesting the region of interest (ROI). Thus the sheep should be slaughtered and not euthanized. That way their bodies can at least be used for animal food (e.g. zoo animals).

As gap formation and healing are dynamic processes, it is important to evaluate the model at different time points. Three animal groups with 4, 8 and 12 weeks survival time would best reflect representative stages of tendon healing and allow tracking and judging gap formation. When planning animal group size, it is important to clarify

either histology or biomechanical testing as primary outcome. Those are not mutually exclusive per se, however biomechanical testing is a destructive (or at least partially destructive) assessment method and limits the potential of histology dramatically. If both methods should contribute equally to the final picture, it is important to split each survival time group in histology- and biomechanical test animals. Statistical power is also an important aspect to consider when choosing group size and depends on the rate of success of a procedure as well as the estimated difference between control and test outcomes and the inherent variability of those outcomes.

Four weeks after repair, the model will mainly provide insight into tissue response. At this time point, the macroscopic evaluation of the repair site and the surrounding tissues will be the primary outcome. Signs of inflammation or necrosis of the subcutaneous tissue, the adjacent muscles and the tendon itself must be evaluated. Possible excessive fibrosis formation and scar tissue can be assessed and evaluated. The extent of suture cheese wiring must be evaluated and can provide information about the success of repair unloading strategies (release cut, suspension system). Measuring the marker distances will show gap size changes and allow a first evaluation of the model functionality and gap size development. Histology of the tendon at this time point will mainly allow the evaluation of the biocompatibility of biomaterials used for repair and show the composition of early healing tissue. Biomechanical testing after 4 weeks can be performed but should be a secondary outcome as it can be assumed that this time point is too early for a resilient tendon healing to take place.

After 8 weeks, macroscopic evaluation of the ROI will most likely show a reduction of the acute response and the transition to an active organization of the affected tissues. The measurements of the marker distances will allow comparison with previous results and provide information about gapping at this stage. The condition of the tendon will provide important information as well, particularly predictive information as to the fate of tendon healing. Histology in this context can confirm tendon improvement or irreversible tendon damage. Potentially a first look at collagen type and fiber alignment can provide information about the timing of tendon healing. In combination with the indicator distance measures, histology results could already allow the determination of a critical gap size. Biomechanical testing at this time point is a helpful tool to underline and complement macroscopic and histologic findings. The strength of the healed tendon at this time point is a good indicator of healing kinetics.

At 12 weeks, healing kinetics are expected to reach a plateau. That is also the time when tissue remodeling is expected to start as the healed tissue matures. The development of mechanical resistance in comparison to the 8-week group will indicate if appropriate strengthening has taken place and can be complemented with histologic findings to indicate the level of maturation of the healed tissue.

7.4 Assessment methods

7.4.1 Macroscopic evaluation

Section 1 - *First impression*				
Hematoma	**O** yes	**O** no		
Inflammation	**O** none	**O** mild	**O** moderate	**O** severe
Tendon	**O** visible	**O** non-visible		
Fibrosis	**O** mild	**O** moderate	**O** severe	
Section 2 - *Tendon exposed*				
Tendon	**O** intact	**O** torn		
Tendon thickness	**O** normal	**O** thinner	**O** thicker	
Gap	**O** visible	**O** non-visible		
Suture	**O** intact	**O** torn		
Cheese wiring	**O** none	**O** mild	**O** moderate	**O** severe
Inflammation at stitch	**O** none	**O** mild	**O** moderate	**O** severe
Knot security at plate	**O** firm	**O** loose	**O** open	
Proximal bone tunnels	**O** normal	**O** widenend		
Section 3 - *Measures*	(in milimeter)			
Distance steel wire- marker screw				
Length marking suture				
Gap width (if gap visible)				
Tendon width proximal				
Tendon width distal				
Comments:				

Figure 7.2*: Macroscopic evaluation, the applicable is checked, measures are noted in millimeter, and further observations are written under "comments"*

Once an animal is slaughtered, the operated front limb is separated from the thorax with a long cut medial to the scapula. After the skin is removed, the fascia is incised and the ROI is carefully approached. A protocol (Figure 7.2) was created to provide a standardized macroscopic evaluation. It is composed of three parts: The first is a general

impression of the surrounding soft tissues. Signs of inflammation or hematoma are evaluated as well as the extent of fibrosis. The second part takes closer look to the tendon and the repair site. Here it is evaluated whether the tendon and the sutures are still intact. Also the visual condition of the tendon and potential tendon affection by the sutures is taken into account. The gap is visualized if possible. Furthermore the knot security of the sutures is tested and the position of the 8-hole plate assessed for slippage. For assessing the tendon stitches and proximal bone tunnel entrances, it might be necessary to release the infraspinatus muscle and look at the tendon from the medial side. In the last section, the marker distances, proximal and distal tendon width and if possible the gap width is measured.

Findings that are not covered with the protocol are separately noted. Depending on the further assessment method it is thus necessary to cover the tendon with 0.9 % saline solution soaked gauze to keep it moist and preserve the tissue. The extent of the destructive dissection process must be limited to a reasonable level, which is determined by the preconditions for subsequent assessment methods.

7.4.2 Biomechanical testing

***Figure 7.3**: Biomechanical test set-up*

To test the biomechanical properties of the healed tendon, a special set-up is needed. After careful and non-destructive macroscopic assessment, the specimens need to be prepared for the test. Therefore the infraspinatus muscle is transversally cut approximately 3-4 cm proximal to the musculotendinous junction and the muscle tissue is laterally and medially removed until the central tendon becomes visible. The scapulohumeral joint is opened and the proximal humerus is separated from all other muscles and tendons. Finally, the humerus diaphysis is also freed from all adjacent muscles and cut transversally just proximal to the elbow. The cut end is then potted into a plastic ring, for example with Polymethylmethacrylat (PMMA), which has proven to provide sufficient strength. It is important to pot a reasonable length of the bone but at the same time also avoiding impingement of the tendon clamp with the humerus fixation device. In order to also avoid impingement of the tendon clamp with the humeral head it might be necessary to partially resect the humeral head.

Prior to testing it is necessary to release the intact half of the tendon right at the footprint. That way only the previously repaired zone is tested. This step is essential as we found in preliminary tests that only 25% of the intact infraspinatus tendon can withstand higher forces than the humerus in this setup. Also it is necessary to release the four sutures between the 8-hole plate and the bone. By detaching the sutures it can be ensured that only the healed area is effectively weight bearing, when traction is applied to the tendon. A cryo clamp provides best tendon fixation. This is a clamp with a small bucket attached to each side, which can be filled with dry ice. In combination with pressure fixation of the two interdigitating sides of the clamp, the adhesion caused by the temperature gradient, results in excellent hold of the tendon. The specimen is clamped in a way that at least 3 cm of the tendon are grasped. After positioning the potted humerus perpendicular to the direction of traction, it is also important to ensure exact positioning of the humeral axis in order to mimic the physiological direction of force (Figure 7.3).

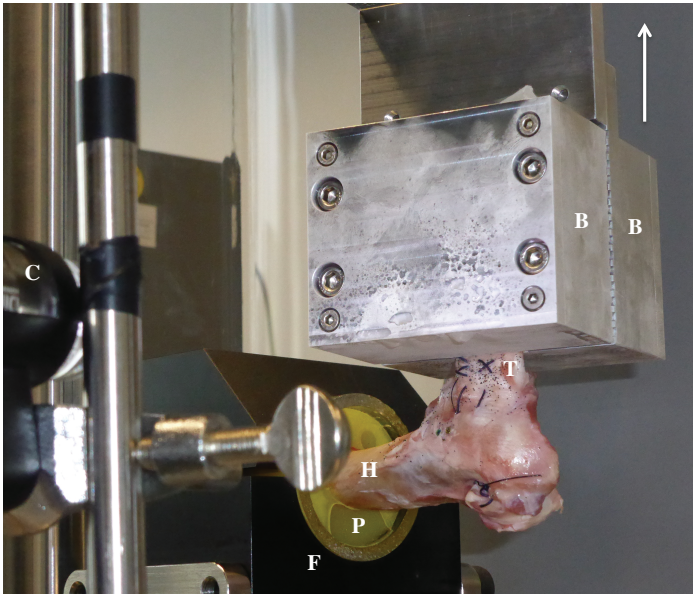

Figure 7.3: *Close-up of the test set-up.* ***T*** *repaired infraspinatus tendon clamped between the* ***B*** *cryo clamp buckets (filled with dry ice),* ***H*** *humerus potted with* ***P*** *PMMA into plastic cylinder, which is held by* ***F*** *fixation device,* ***C*** *camera monitoring of the test, arrow depicts direction of traction.*

A digital temperature probe is attached to one of the clamp buckets. Testing can start when the measured temperature drops below 0° Celsius. It is important to ensure that the test is started before the non-clamped part of the tendon freezes. The temperature drops quickly and if the healed area freezes, this is likely to alter the specimen's ultimate strength.

The cryo clamp is mounted to a 10 Kilonewton load cell, which is part of the "Instron" test machine (Instron ElectroPuls E10000 Linear-Torsion). The biomechanical testing mainly consists of 4 steps. After tuning the machine to the specimen's individual stiffness, the tension on the specimen is increased at a rate of 1 N/s until 20 N are reached. Then the load of 20 N is maintained for 120 seconds. This step is followed by 10 seconds of cyclic loading, with the force undulating between 10 and 30 N. Finally the crosshead slowly displaces upwards at rate of 1mm/s, until the tendon ruptures off the bone. The load at the time point of rupture reflects the ultimate strength of the healed tissue. Small metal beads can be placed on the tendon for visually tracking the tissue movement with a microscope camera.

7.4.3 Histology

Although biomechanical testing partially destroys the healed portion of the tendon, the proximal aspect of the tested tendon can still be used for histology, if one is aware of the artifacts that will be found due to the biomechanical testing and freezing.

As tendon is a very stiff and solid tissue and also the suture materials for tendon repair are very rigid, only thick section Methyl-Methacrylat (MMA) histology is feasible. Thick section histology of the tendon-suture interface allows evaluating the involved cells, detecting potential foreign body reaction and assessing the extent of cheese wiring. The latter might be biased due to mechanical testing artifacts; however, the biological effects of cheese wiring on the surrounding tissue and cells may be assessed.

Prior to MMA embedding and cutting, proper fixation of the tendons is needed. First, the tendons are kept in buffered 4% Formalin for about ten days. Then the specimen is thoroughly cleaned with tap water for at least 3 x 20 minutes. Afterwards the gradual dehydration process starts with graded forms of ethanol. When the specimen is completely dehydrated in 100% ethanol, it is kept in Xylol under a vacuum for 4 days with one change of the Xylol in between. Finally, the specimen is embedded in MMA and, once this has hardened, the sections can be cut.

Depending on the target, different staining needs to be chosen. For thick sections a Giemsa staining has proven well to differentiate tendon and fibrous tissue and show cellular aspects. Generally Hämatoxylin Eosin (HE) staining has not been very well established in thick sections. However, this staining can potentially be used to further differentiate tissue reactions on the cellular level in thin sections.

When the assessment of biocompatibility of a novel suture material is planned, paraffin thin section histology of the shoulder lymph nodes (Lymphonodi craniales superficiales) should be considered. When histology is chosen to be the major outcome and there was no biomechanical testing before, of course there are many more options to be considered. For example Picrosirius Red staining of the healing tendon and surrounding fibrosis enables to identify collagen fibers and their alignment. This information is very helpful to track the timing of healing and tissue reorganization. Also thick section histology of the tendon insertion into the footprint would provide important information regarding biological healing at the predominant site of failure.

7.5 Potential limitations

The model design, although very useful, still has some notable limitations. A factor that seems somewhat unpredictable is that sheep tend to develop an excessive healing callous. Previous studies performing an infraspinatus tenotomy in sheep encountered excessive formation of tendon-like scar tissue ("neotendon") [150, 152]. Thus it could be difficult to locate the gap size markers and also challenging to take accurate measurements post mortem. Furthermore the created gap might be filled with scar tissue and it is unclear whether it will still be visible on the day of macroscopic assessment. Although intraoperative placement of a strain-reducing release cut and also postoperative suspension of the animals is intended to further decrease the repair load, it is unclear how much force acts on the repair site. Of course gap formation is tension dependent and, as this model is designed to assess the behavior and effects of gap formation, some tension is wanted. Controlling the level of tension is however challenging, as sheep, in some respects, are less cooperative than humans.

A limitation of the radiographic gap tracking might be a lack of positioning reproducibility. Correlations of the intraoperatively measured distances with immediate post-operative radiographs and also of a post mortem radiographs and the distances measured at the macroscopic evaluation will allow to validate the accuracy of this method. It may also be helpful to implant more markers in order to account for plane variation in imaging.

As described above, in the process of preparing the specimens for biomechanical testing it is inevitable to resect the remaining cranial intact half of the tendon, when one chooses to assess the new tissue mechanics alone. This however might be difficult to achieve, as the repaired and intact portions might not be clearly distinguishable. It is likely that either too much or too little of the cranial portion will be resected. Subsequently this will influence the biomechanical strength. Biomechanically testing the whole tendon, without resecting the intact portion, may therefore circumvent this limitation, however then the lever of the humerus needs to be minimized in order to prevent bone fracture before the tendon ruptures.

7.6 Conclusion

The presented ovine model is an attempt to create a suitable large animal model, that allows filling the gap between cadaver studies and human clinical trials. It provides many assessment options and can be varied for different purposes. From an ethical stand point it is justifiable as long as the principles of animal trials are maintained. It should always be the primary goal to assess as many research questions as possible in an animal trial, as healthy living creatures are sacrificed for scientific purpose.

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9 Glossary

AIC	Aikake Information Criterion
ASES	American Shoulder and Elbow Surgeons
BIC	Bayesian Information Criterion
CSA	Critical Shoulder Angle
CT	Computer Tomography
CT-A	Computer Tomography Arthography
DR	Double Row Repair
MRI	Magnet Resonance Imaging
MTJ	Musculotendinous Junction
PG	Patient Group
PMMA	Polymethylmethacrylat
RCR	Rotator Cuff Repair
RCT	Rotator Cuff Tear
ROI	Region of Interest
ROM	Range of Motion
SR	Single Row Repair
TOE	Transosseus equivalent Repair
UCLA	University of California Los Angeles
UHMWPE	Ultra High Molecular Weight Polyethylene
US	Ultrasound
VAS	Visual Analog Scale

10 Appendix

10.1 Supplementary data Chapter 4

Patient Group	Shoulders	Fatty Infiltration	Tendon retraction (mm)	Tear size (mm)
PG 1	52	NR	NR	24.7 (no SD), incl. 10-40
PG 2	80	Excl. Fuchs grade 4	NR	25.3±8.3 ; Small (51), Large (29)
PG 3	80	Excl. Fuchs grade 4	NR	26.2±7.4 ; Small (53), Large (27)
PG 4	87	50 GFDI 0.25-1.0, 19 GFDI 1.0-1.5, 7 GFDI 1.5-2.0, 12 >GFDI 2	NR	small(7),medium(41),large(32), massive(7)
PG 5	271	1.35 GFDI (0-2 included)	NR	medium (101), large(170)
PG 6	147	29 G1, 67 G2, 40 G3, 11 G4, Goutallier	NR	medium (94), large (38), massive (15)
PG 7	55	0.54± 0.61(GFDI), split by tendon	NR	small (21), 34 partial thickness tears
PG 8	39	NR	23 P1, 15 P2, 1 P3	25 mean, incl. 18-40
PG 9	135	excl. > 3 Goutaillier	excl. Patte 3	NR
PG 10	25	NR	NR	NR
PG 11	113	49 G0, 54 G1, 10 G2 Goutallier	NR	21.7 ± 0.67 incl. 10-40
PG 12	116	NR	13.7	14.4
PG 13	73	NR	NR	medium (50), large (14), massive (9)
PG 14	25	NR	20.9	23.5, incl. 10 to 40
PG 15	25	NR	20.8	23.3, incl. 10 to 40
PG 16	56	NR	18.3±13.2	18.9±12.6, incl. <30
PG 17	49	NR	17.8±12.9	16.3±6.5, incl. <30
PG 18	24	1.2±0.4 (GFDI)	21.0±6.3	17.2±5.7
PG 19	23	1.2±0.4 (GFDI)	20.8±5.6	17.5±6.2
PG 20	40	1.2±0.6 (GFDI), split by tendon	23.7±8.4	19.4±7.6 , incl. 20 to 40
PG 21	48	1.1±0.5 (GFDI), split by tendon	21.9±9.6	19.7±8.7, incl. 20 to 40
PG 22	105	NR	36 P1, 47 P2,22 P3	all sizes included
PG 23	39	Excl. ≥ 3 Goutallier	21.4 ± 9.4	18.9 ± 8.5
PG 24	34	Excl. ≥3 Goutallier	23.8 ± 10.8	18.9 ± 6.6
PG 25	1000	NR	15 (3-80)	18 (3-80)
PG 26	27	NR	NR	70.4% (< 30), 29.6% (>30), excl. < 10
PG 27	26	NR	NR	65.4% (<30), 34.6% (>30), excl. < 10
PG 28	22	NR	NR	incl. > 30
PG 29	107	Excl. ≥ 3Goutallier	excl. Patte 3	Excl. Massive tears
PG 30	86	NR	NR	33 ± 15, (10-70)
PG 31	78	incl. all Goutallier grades	1.63±1.04	small(11), medium(32), large(18), massive(17)
PG 32	95	1.3±0.82 (GFDI)	26.1±7.8	36.3 ±5.8 incl. 30-50
PG 33	40	0.45± 0.7	21 (5-45)	29 (25-51)
PG 34	86	NR	NR	small(26), medium(30), large(22),massive(8)
PG 35	49	NR	NR	small-medium(24),large-massive(25)
PG 36	154	incl. ≤ 2 Goutallier	47 P1,88 P2,19 P3	NR
PG 37	45	NR	21 P1,22 P2,4 P3	NR
PG 38	55	NR	NR	excl. <10

Table A 4.1 *depicts the great differences in the reporting of fatty infiltration, tendon retraction and tear size throughout the analyzed studies.*

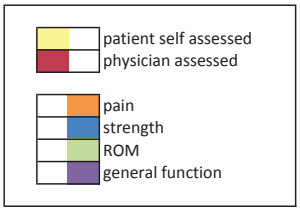

***Figure A 4.1**: Color code for clinical score analysis (Figures A4.2-A4.4)*

Constant score *(Total 100)*

1- Pain *(15)*

O severe
O moderate
O mild
O none

2- Activity level *(10)*

O yes / **O** no unaffected sleep
O yes / **O** no full reacreation/ sport
O yes / **O** no full work

3- Arm positioning *(10)*

O up to waist
O up to xiphoid
O up to neck
O up to top of head
O above head

4- Strength of abduction (lbs.) *(25)*

O 0
O 1-3
O 4-6
O 7-9
O 10-12
O 13-15
O 16-18
O 19-21
O 22-24
O > 24

5 - Forward flexion *(10)*
6- Lateral elevation *(10)*

5	**6**
O 31°-60°	**O** 31°-60°
O 61°-90°	**O** 61°-90°
O 91°-120°	**O** 91°-120°
O 121°-150°	**O** 121°-150°
O 151°-180°	**O** 151°-180°

7- External rotation *(10)*

O hand behind head, elbow forward
O hand behind head, elbow back
O hand to top of head, elbow forward
O hand on top of head, elbow back
O full elevation

8- Internal rotation *(10)*

O lateral thigh
O buttock
O lumbosacral junction
O waist (L3)
O T 12 Vertebra
O Interscapular (T7)

Figure A 4.2: *Constant score components, analyzed for assessment type (patient self vs. physician) and category (pain, strength, ROM, general function).*

UCLA score (*Total 35*)

1 - Pain *(10)*

O present always an unbearable; strong medication frequently
O present always but bearable ; strong medication occasionally
O none or little at rest; present during light activities; NSAIDs used frequently
O occasional and slight
O none

2 - Function *(10)*

O unable to use limb
O only light activities possible
O able to do light housework or most activities of daily living
O most housework, shopping and driving possible; able to do hair and to dress and undress
O slight restriction only
O normal activities

3 - Active forward flexion *(5)*

O 150°
O 120°-150°
O 90°-120°
O 45°-90°
O 30°-45°
O < 30°

4 - strength of forward flexion *(5)* **(manual muscle testing)**

O Grade 5 (normal)
O grade 4 (good)
O grade 3 (fair)
O grade 2 (poor)
O grade 1 (muscle concentration)
O grade 0 (nothing)

5 - satisfaction of patient *(5)*

O satisfied and better
O not satisfied and worse

Figure A 4.3: *UCLA score components, analyzed for assessment type (patient self vs. physician) and category (pain, strength, ROM, general function).*

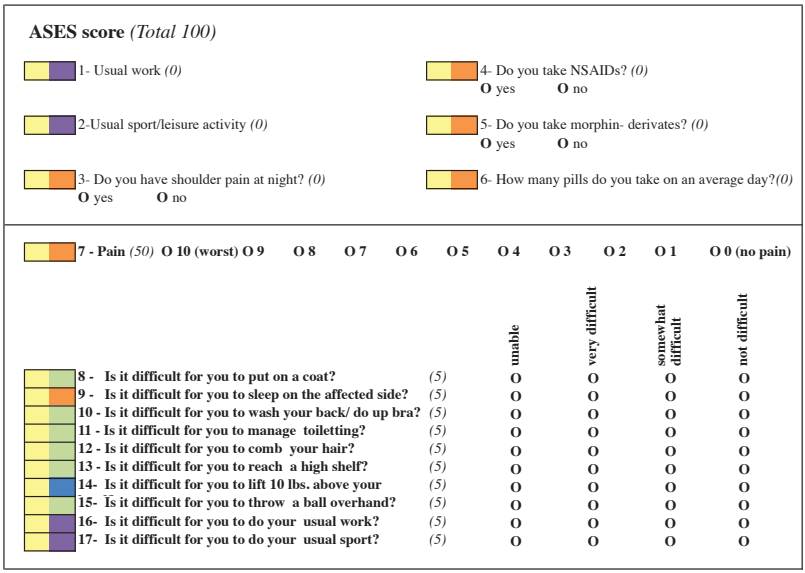

Figure A 4.4: *ASES score components, analyzed for assessment type (patient self vs. physician) and category (pain, strength, ROM, general function).*

Patient group	Shoulders	Mean patient age	Proportion male patients	Pre-op Constant score	Pre-op ASES score	Pre-op UCLA score	Pre-op VAS pain	Proportion TOE repairs	Proportion DR repairs	Proportion SR repairs	Proportion FiberWire	Proportion biobabsorb. anchors	Rehab category "active ROM"	Rehab category "onset strengthening"
PG 1	52	58.3	0.63	NR	NR	NR	NR	0	1	0	NR	1	NR	0
PG 2	80	55.8	0.44	NR	NR	NR	NR	0	0	1	1	1	0	0
PG 3	80	55.2	0.41	NR	NR	NR	NR	0	1	0	1	1	0	0
PG 4	87	55.4	0.49	48	NR	13.2	6.2	1	0	0	1	1	1	NR
PG 5	271	58.2	0.52	63.82	NR	16.59	5.01	1	0	0	1	1	1	NR
PG 6	147	62.8	0.44	53.3	NR	14	NR	1	0	0	1	1	1	NR
PG 7	55	57.9	0.36	NR	45.85	18.28	7.35	0.55	0	0.45	0.5	1	0	0
PG 8	39	54	0.62	NR	42.23	NR	6.55	0	0	1	0	0	1	1
PG 9	135	73.9	0.46	44.4	35.44	NR	NR	0	0.5	0.5	NR	NR	NR	NR
PG 10	25	57.1	0.52	NR	NR	NR	NR	1	0	0	1	1	1	1
PG 11	113	58.7	0.59	61.3	NR	NR	5.54	1	0	0	0.5	NR	NR	1
PG 12	116	55.3	0.6	54.5	45	NR	5.61	0	1	0	1	0	1	1
PG 13	73	58.3	0.61	52.7	50.4	21.6	6.6	1	0	0	1	1	1	1
PG 14	25	57.46	0.62	50.63	48.5	19.54	5.54	0	1	0	1	0.5	1	1
PG 15	25	58.96	0.54	58.73	58	21.46	4.2	1	0	0	1	1	1	1
PG 16	56	60.06	0.46	53.73	48.38	NR	NR	0.82	0.02	0.16	1	1	NR	0
PG 17	49	60	0.37	49.93	46.27	NR	NR	0.82	0.02	0.16	1	1	NR	0
PG 18	24	61.6	0.29	61.4	38.8	18	5.8	0	0	1	1	0.64	NR	1
PG 19	23	61.1	0.35	63.5	38.1	17.7	5.8	0	1	0	1	0.58	NR	1
PG 20	40	NR	NR	50.9	44.4	NR	5.8	0	0	1	1	1	0	0
PG 21	48	NR	NR	54.2	45.8	NR	5.6	0	0	1	1	1	1	1
PG 22	105	52	0.49	43.2	NR	NR	6.87	0	1	0	0	0	1	NR
PG 23	39	56	0.73	55.1	47.8	NR	NR	0	0	1	0	0.5	1	1
PG 24	34	57.8	0.69	58.2	54	NR	NR	0	1	0	0	0.5	1	1
PG 25	1000	59	0.55	NR	NR	NR	NR	0	0	1	NR	0	1	1
PG 26	27	60.8	0.56	NR	40.81	10.85	NR	0	0	1	0	0	1	0
PG 27	26	61.6	0.54	NR	40.8	11.38	NR	0	1	0	0	0	1	0
PG 28	22	63.7	0.50	NR	NR	NR	NR	1	0	0	1	0	1	1
PG 29	107	54.8	0.61	54.5	NR	NR	5.33	1	0	0	0	0	NR	1
PG 30	86	59.1	0.58	NR	52.8	NR	NR	0	0.56	0.44	0	NR	NR	NR
PG 31	78	59.2	0.63	NR	42.1	NR	5.83	1	0	0	1	1	0	0
PG 32	95	60.7	0.41	51.74	47.68	NR	5.39	1	0	0	1	1	1	0
PG 33	40	61.4	0.58	NR	NR	NR	NR	1	0	0	1	1	1	1
PG 34	86	60.5	0.60	NR	42.3	14.5	NR	0	1	0	NR	0	0	0
PG 35	49	59	0.53	NR	45.48	NR	5.93	0	1	0	1	0	1	1
PG 36	154	NR	0.54	44.44	NR	NR	7.45	1	0	0	1	1	NR	1
PG 37	45	62	0.63	58	NR	NR	NR	1	0	0	1	0	1	1
PG 38	55	53.9	0.51	NR	39.55	10.01	NR	0	0	1	0	1	0	NR

***Table A 4.2a**: Detailed data used for statistical analyses*

Patient group	Proportion ultrasound assessment	Imaging time point (months)	Mean last follow-up exam. (months)	Re-tear rate (%)	Re-torn cuffs	Medial failure rate (%)	Medial failures	Post-op Constant score	Post-op Constant score SD	Post-op ASES score	Post-op ASES score SD	Post-op UCLA score	Post-op UCLA score SD	Post-op VAS pain	Post-op VAS pain SD
PG 1	1	30	30	17.31	9	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
PG 2	0	24	24	18.8	15	NR	NR	77.50	6.66	82.45	6.06	28.00	2.21	NR	NR
PG 3	0	24	24	10	8	NR	NR	78.35	2.92	84.20	3.13	28.85	1.52	NR	NR
PG 4	0	8.5	25.2	33.33	29	58.6	17	80.3	NR	NR	NR	29.7	NR	0.4	NR
PG 5	0	7.2	27.2	14.39	39	NR	NR	85.17	5.37	NR	NR	33.24	2.18	0.98	1.02
PG 6	0	23.4	31.2	17.01	25	80	20	84.3	NR	NR	NR	30.4	NR	NR	NR
PG 7	0	6	24	27.27	15	NR	NR	NR	NR	91.58	10.8	27.4	2.32	0.68	0.92
PG 8	0	23	NR	12.82	5	NR	NR	NR	NR	89.43	NR	NR	NR	1.35	NR
PG 9	1	12	12	18.52	25	NR	NR	76	NR	90	NR	NR	NR	NR	NR
PG 10	0	14.6	NR	12.00	3	NR	NR	84.29	NR	93.04	NR	30.59	NR	NR	NR
PG 11	0	NR	12	16.81	19	NR	NR	93.99	10.65	NR	NR	NR	NR	0.58	1.3
PG 12	1	12	24	8	9	NR	NR	83.9	11.2	92.4	13.3	NR	NR	0.61	1.4
PG 13	0.89	24	30.6	15.07	11	27.3	3	74.7	13.21	86.2	17.67	30.9	4.7	1.6	NR
PG 14	0.84	34.3	37	24	6	33.3	2	80.71	7.38	90.5	10.12	32.25	2.17	2.08	0.88
PG 15	0.84	31.7	37	20	5	40	2	73.96	15.39	88.46	15.67	30.58	5.87	1.8	2.27
PG 16	0	12	12	12.5	7	NR	NR	69.81	7.47	73.29	56.16	NR	NR	2.8	NR
PG 17	0	12	12	18.3	9	NR	NR	69.83	13.47	82.9	27.53	NR	NR	1.8	NR
PG 18	0	27.4	24	16.6	4	NR	NR	85.5	12.7	84.3	15.5	29.5	4.4	1.8	2
PG 19	0	27.6	24	26.1	6	NR	NR	85.7	20.2	84.6	22	30.1	6.5	1.9	2.5
PG 20	0	24	24	12.5	5	NR	NR	85.6	15.6	88.9	16.2	NR	NR	1.3	1.8
PG 21	0	24	24	8.3	4	NR	NR	88.7	9.7	92.1	10.2	NR	NR	0.8	1
PG 22	0	23	24	11.43	12	NR	NR	80.1	11.1	NR	NR	NR	NR	1.47	2
PG 23	0.5	NR	24	33	13	NR	NR	85.6	14	87.9	16.9	NR	NR	NR	NR
PG 24	0.5	NR	24	22	7	NR	NR	86.3	14.2	89.3	17.5	NR	NR	NR	NR
PG 25	1	6	NR	17.40	174	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
PG 26	0	33.3	33.3	22.2	6	NR	NR	NR	NR	91.25	2.36	31.4	3.34	NR	NR
PG 27	0	33.5	33.5	11.5	3	NR	NR	NR	NR	91.38	2.36	31.53	3.4	NR	NR
PG 28	1	NR	24	40.91	9	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
PG 29	0	16	16.1	10.28	11	9.1	1	80	12.1	NR	NR	NR	NR	1.33	1.67
PG 30	1	NR	24	26.74	23	NR	NR	NR	NR	91.36	13.42	NR	NR	NR	NR
PG 31	1	NR	12	8.97	7	NR	NR	NR	NA	91.9	8.81	NR	NR	0.65	0.94
PG 32	1	NR	24	17.89	17	64.7	11	76.8	10.54	88.48	13.01	NR	NR	1.4	1.75
PG 33	0	16.1	12	17.50	7	NR	NR	NR	NR	91.22	13.38	NR	NR	NR	NR
PG 34	0	14	31	17.44	15	NR	NR	NR	NR	94.3	9.7	32.9	3.7	NR	NR
PG 35	1	16	29	48.98	24	NR	NR	NR	NR	82.39	17.89	NR	NR	2.06	2.05
PG 36	0	15	15	14.29	22	NR	NR	80.47	9.3	NR	NR	NR	NR	1.49	1.87
PG 37	0	12	24	28.89	13	46	6	88	NR	NR	NR	NR	NR	NR	NR
PG 38	0	28.8	28.8	36	20	NR	NR	NR	NR	91.34	5.22	30.94	5.57	NR	NR

***Table A 4.2b**: Detailed data used for statistical analyses*

10.2 Supplementary data chapter 6

Patient group	Shoulders	Mean age	Proportion male patients	Pre-op Constant score	Pre-op ASES score	Pre-op UCLA score	Pre-op VAS pain	Proportion of TOE repairs	Proportion of DR repairs	Proportion of SR repairs	Proportion of FiberWire use	Biobuttress anchors	Active ROM Onset	Onset strengthening	Ultrasound Assessment	Imaging time point	Mean Last clinical follow up	Re-tear rate in %	Re-torn cuffs	Medial failure rate in %	Medial failures	Post-op Constant score	Post-op Constant score SD	Post-op ASES score	Post-op ASES score SD	Post-op UCLA score	Post-op UCLA score SD	Post-op VAS pain	Post-op VAS pain SD	% Reporting per patient group
PG 1	52	58.3	0.63	NR	NR	NR	NR	0	1	0	NR	1	NR	0	1	30	30	17.31	9	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	45%
PG 2	80	55.8	0.44	NR	NR	NR	NR	0	0	1	1	1	0	0	0	24	24	18.8	15	NR	NR	77.50	6.66	82.45	6.06	28.00	2.21	NR	NR	72%
PG 3	80	55.2	0.41	NR	NR	NR	NR	0	1	0	1	1	0	0	0	24	24	10	8	NR	NR	78.35	2.92	84.20	3.13	28.85	1.52	NR	NR	72%
PG 4	87	55.4	0.49	48	NR	13.2	6.2	1	0	0	1	1	1	NR	0	8.5	25.2	33.33	29	58.6	17	80.3	NR	NR	NR	29.7	NR	0.4	NR	76%
PG 5	271	58.2	0.52	63.82	NR	16.59	5.01	1	0	0	1	1	1	NR	0	7.2	27.2	14.39	39	NR	NR	85.17	5.37	NR	NR	33.24	2.18	0.98	1.02	79%
PG 6	147	62.8	0.44	53.3	NR	14	NR	1	0	0	1	1	1	NR	0	23.4	31.2	17.01	25	80	20	84.3	NR	NR	NR	30.4	NR	NR	NR	69%
PG 7	55	57.9	0.36	NR	45.85	18.28	7.35	0.55	0	0.45	0.5	1	0	0	0	6	24	27.27	15	NR	NR	NR	NR	91.58	10.8	27.4	2.32	0.68	0.92	83%
PG 8	39	54	0.62	NR	42.23	NR	6.55	0	0	1	0	0	1	1	0	23	NR	12.82	5	NR	NR	NR	NR	89.43	NR	NR	NR	1.35	NR	62%
PG 9	135	73.9	0.46	44.4	35.44	NR	NR	0	0.5	0.5	NR	NR	NR	NR	1	12	12	18.52	25	NR	NR	76	NR	90	NR	NR	NR	NR	NR	52%
PG 10	25	57.1	0.52	NR	NR	NR	NR	1	0	0	1	1	1	1	0	14.6	NR	12.00	3	NR	NR	84.29	NR	93.04	NR	30.59	NR	NR	NR	59%
PG 11	113	58.7	0.59	61.3	NR	NR	5.54	1	0	0	0.5	NR	NR	1	0	NR	12	16.81	19	NR	NR	93.99	10.65	NR	NR	NR	NR	0.58	1.3	62%
PG 12	116	55.3	0.6	54.5	45	NR	5.61	0	1	0	1	0	1	1	1	12	24	8	9	NR	NR	83.9	11.2	92.4	13.3	NR	NR	0.61	1.4	83%
PG 13	73	58.3	0.61	52.7	50.4	21.6	6.6	1	0	0	1	1	1	1	0.89	24	30.6	15.07	11	27.3	3	74.7	13.21	86.2	17.67	30.9	4.7	1.6	NR	97%
PG 14	25	57.46	0.62	50.63	48.5	19.54	5.54	0	1	0	1	0.5	1	1	0.84	34.3	37	24	6	33.3	2	80.71	7.38	90.5	10.12	32.25	2.17	2.08	0.88	100%
PG 15	25	58.96	0.54	58.73	58	21.46	4.2	1	0	0	1	1	1	1	0.84	31.7	37	20	5	40	2	73.96	15.39	88.46	15.67	30.58	5.87	1.8	2.27	100%
PG 16	56	60.06	0.46	53.73	48.38	NR	NR	0.82	0.02	0.16	1	1	NR	0	0	12	12	12.5	7	NR	NR	69.81	7.47	73.29	56.16	NR	NR	2.8	NR	72%
PG 17	49	60	0.37	49.93	46.27	NR	NR	0.82	0.02	0.16	1	1	NR	0	0	12	12	18.3	9	NR	NR	69.83	13.47	82.9	27.53	NR	NR	1.8	NR	72%
PG 18	24	61.6	0.29	61.4	38.8	18	5.8	0	0	1	1	0.64	NR	1	0	27.4	24	16.6	4	NR	NR	85.5	12.7	84.3	15.5	29.5	4.4	1.8	2	90%
PG 19	23	61.1	0.35	63.5	38.1	17.7	5.8	0	1	0	1	0.58	NR	1	0	27.6	24	26.1	6	NR	NR	85.7	20.2	84.6	22	30.1	6.5	1.9	2.5	90%
PG 20	40	NR	NR	50.9	44.4	NR	5.8	0	0	1	1	1	0	0	0	24	24	12.5	5	NR	NR	85.6	15.6	88.9	16.2	NR	NR	1.3	1.8	76%
PG 21	48	NR	NR	54.2	45.8	NR	5.6	0	0	1	1	1	1	1	0	24	24	8.3	4	NR	NR	88.7	9.7	92.1	10.2	NR	NR	0.8	1	76%
PG 22	105	52	0.49	43.2	NR	NR	6.87	0	1	0	0	0	1	NR	0	23	24	11.43	12	NR	NR	80.1	11.1	NR	NR	NR	NR	1.47	2	69%
PG 23	39	56	0.73	55.1	47.8	NR	NR	0	0	1	0	0.5	1	1	0.5	NR	24	33	13	NR	NR	85.6	14	87.9	16.9	NR	NR	NR	NR	69%
PG 24	34	57.8	0.69	58.2	54	NR	NR	0	1	0	0	0.5	1	1	0.5	NR	24	22	7	NR	NR	86.3	14.2	89.3	17.5	NR	NR	NR	NR	69%
PG 25	1000	59	0.55	NR	NR	NR	NR	0	0	1	NR	0	1	1	1	6	NR	17.40	174	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	45%
PG 26	27	60.8	0.56	NR	40.81	10.85	NR	0	0	1	0	0	1	0	0	33.3	33.3	22.2	6	NR	NR	NR	NR	91.25	2.36	31.4	3.34	NR	NR	72%
PG 27	26	61.6	0.54	NR	40.8	11.38	NR	0	1	0	0	0	1	0	0	33.5	33.5	11.5	3	NR	NR	NR	NR	91.38	2.36	31.53	3.4	NR	NR	72%
PG 28	22	63.7	0.50	NR	NR	NR	NR	1	0	0	1	0	1	1	1	NR	24	40.91	9	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	48%
PG 29	107	54.8	0.61	54.5	NR	NR	5.33	1	0	0	0	0	NR	1	0	16	16.1	10.28	11	9.1	1	80	12.1	NR	NR	NR	NR	1.33	1.67	76%
PG 30	86	59.1	0.58	NR	52.8	NR	NR	0	0.56	0.44	0	NR	NR	NR	1	NR	24	26.74	23	NR	NR	NR	NR	91.36	13.42	NR	NR	0.65	NR	48%
PG 31	78	59.2	0.63	NR	42.1	NR	5.83	1	0	0	1	1	0	0	1	NR	12	8.97	7	NR	NR	NR	NR	91.9	8.81	NR	NR	0.65	0.94	72%
PG 32	95	60.7	0.41	51.74	47.68	NR	5.39	1	0	0	1	1	1	0	1	NR	24	17.89	17	64.7	11	76.8	10.54	88.48	13.01	NR	NR	1.4	1.75	86%
PG 33	40	61.4	0.58	NR	NR	NR	NR	1	0	0	1	1	1	1	0	16.1	12	17.50	7	NR	NR	NR	NR	91.22	13.38	NR	NR	NR	NR	59%
PG 34	86	60.5	0.60	NR	42.3	14.5	NR	0	1	0	NR	0	0	0	0	14	31	17.44	15	NR	NR	NR	NR	94.3	9.7	32.9	3.7	NR	NR	69%
PG 35	49	59	0.53	NR	45.48	NR	5.93	0	1	0	1	0	1	1	1	16	29	48.98	24	NR	NR	NR	NR	82.39	17.89	NR	NR	2.06	2.05	72%
PG 36	154	NR	0.54	44.44	NR	NR	7.45	1	0	0	1	1	NR	1	0	15	15	14.29	22	NR	NR	80.47	9.3	NR	NR	NR	NR	1.49	1.87	66%
PG 37	45	62	0.63	58	NR	NR	NR	1	0	0	1	0	1	1	0	12	24	28.89	13	46	6	88	NR	NR	NR	NR	NR	NR	NR	66%
PG 38	55	53.9	0.51	NR	39.55	10.01	NR	0	0	1	0	1	0	NR	0	28.8	28.8	36	20	NR	NR	NR	NR	91.34	5.22	30.94	5.57	NR	NR	69%
% Reporting per parameter	100%	92%	95%	58%	61%	34%	50%	100%	100%	100%	89%	92%	74%	82%	100%	82%	92%	100%	100%	21%	21%	66%	55%	71%	63%	42%	34%	55%	42%	

Table A 6.1*: Reporting incidences of all assessed parameters. Blue fields reflect reported data, red fields reflect non-reported/missing data. Grey right column: Percentage of reported data per individual patient group; Grey bottom row: Percentage of reported data in total for individual parameters.*

10.3 Supplementary data chapter 7

10.3.1 Detailed surgery protocol

A 7: Procedure protocol for a partial infraspinatus tenotomy in sheep as a model for gap formation after rotator cuff repair

Surgical sets and materials:

- Othopaedic surgery set
- Drill
- Drillbits 1.5mm and 2.5mm
- Caliper
- Straight surgical needles
- 8-hole button plate
- Size 2 high strength sutures
- 2/0 Supramide® (or equivalent) as shuttle sutures
- 2/0 Supramide® (or equivalent) as marking suture
- 3/0 Steel wire for indicator knot
- 2.0mm x 10mm indicator screw stardrive
- 2/0 Vicryl® (or equivalent) and skin staples for wound closure

Procedure:

The sheep is positioned in left lateral recumbence, the right metacarpus is fixated parallel to the body with the carpus fully flexed. Subsequently the shoulder and elbow joint will be fixated at about 90° flexion.

1. Lateral approach to infraspinatus tendon, skin incision over right shoulder joint, dissection of subcutaneous tissue and fasciae.

2. Preparation of infraspinatus tendon, clear vision of infraspinatus tendon from its insertion into the greater tubercle up to the musculotendinous junction necessary, therefore the deltoideus muscle is partially released and then retracted caudally.

3. **Identification of tendon insertion**, the Metzenbaum scissors are positioned medial to the tendon and pushed distal towards the insertion (***Image 1***), the tendon width is measured just proximal to the insertion.

4. Partial tenotomy, the caudal half of the tendon (exactly 50 % of measured width) is incised perpendicular to the tendon surface just proximal to the insertion (***Image 2***).

5. **Bone tunnel drilling**, 4 tunnels are drilled (2 deep and 2 superficial)
It is started with deep caudal tunnel right below the caudal tendon edge, the drill is positioned on the medial aspect of the greater tubercle and it is aimed for the bicipital grove. **CAVE:** It is important to avoid damage of the biceps tendon. It is then continued with the deep cranial tunnel, starting position is the medial aspect of the greater tubercle right below the cranial end of the incision (mid tendon), the tunnel should be drilled parallel to the first one and exit about 10 -15 mm cranial to it, finally the superficial tunnels are drilled parallel and lateral to the deep.

6. **Insertion of shuttle sutures,** a shuttle suture (2/0 Supramide®) is brought through every bone tunnel, therefore the straight needle is loaded with the suture and inserted head first in the proximal bone hole, then the thread is taken and clamped with a Mosquito from the distal drill hole and the needle then removed from the proximal drill hole (***Image 3***).

7. **Suture placement,** the size 2 high strength sutures are stitched in the tendon (***Image 4)***. First the cranial suture is placed right above the cranial end of the tendon incision, a margin of at least 5 mm to the cut edge must be kept. Afterwards the marking suture (2/0 Supramide®) is placed parallel to the caudal tendon edge, it is started with a simple stitch about 25mm from the cut and then just lies on the tendon. The caudal main suture is then placed around the marking suture. Again it is important to keep a margin of 5mm to the cut edge with the last stitch.

8. Shuttling of the suture threads through the bone tunnels. With help of the shuttle sutures, the 4 main threads (2 deep and 2 superficial) are pulled through their corresponding bone tunnel (***Image 5***). The marking suture shares the tunnel with the caudal superficial thread

9. Proximal tendon incision, to assure a relief of strain on the repair site and with it the functionality of the model, a release cut is placed in the proximal tendon. Therefore the tendon width is measured approx. 5mm proximal to highest stitch of the caudal suture, then the caudal half of the tendon is released ***(Image 6).***

10. Positioning of the 8-hole plate, the 4 threads (+marking suture) are each pulled through one of the holes of the button plate, which is then positioned just proximal to the biceps tendon right on the humerus ***(Image 7).***

11. **Suture knotting**, the two corresponding threads of a suture (deep and superficial) are knotted with first a surgical knot and then 7 half hitches on top of the plate ***(Image 8)***. **CAVE:** it is necessary to knot with moderate force to adjust the tendon gap to 5 mm (***Image 7***). The tip of a needle passer can function as a "gap template" if it was previously measured where it has a width of 5mm. The marking suture is not knotted!

12. Placement of steel wire in the caudal tendon edge, the 3/0 steel wire is passed through the caudal tendon edge approx. 10-15mm proximal to the repair gap with a simple stitch an then knotted (position depicted in ***Image 9***). **CAVE:** it must be avoided to grasp the main suture with the steel wire.

13. Placement of indicator screw, finally the indicator screw (2mm stardrive) is installed. A 1.5mm drill hole is placed in the greater tubercle slightly distal and caudal to the repair site and the screw is inserted (position depicted in ***Image 9***).

14. Measurements
A. Distance from indicator screw (center of screw head) to steel wire knot (***Image 10***).
B. Gap width (should be 5mm, ***Image 11)***
C. Marking suture, cut at length of 20 mm (measured from plate, ***Image 12)***.

15. **Wound closure**

Images 1-12

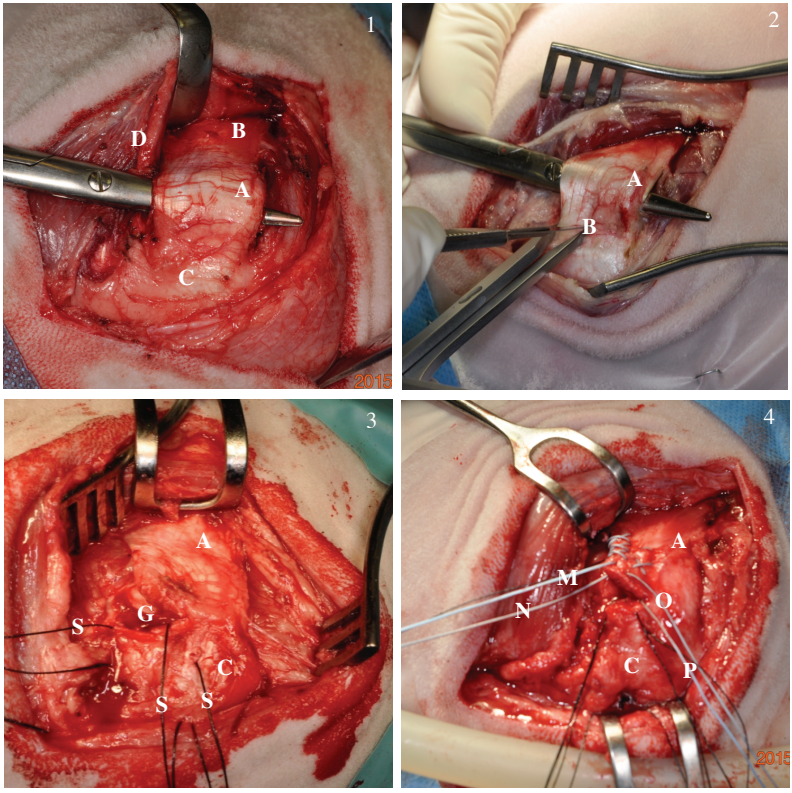

Image 1*: Lateral view of the* ***A*** *infraspinatus tendon,* ***B*** *infraspinatus muscle,* ***C*** *greater tubercle,* ***D*** *deltoid muscle held back with retractor;* ***Image 2****:* ***A*** *infraspinatus tendon,* ***B*** *caudal half of tendon released with scalpel at insertion;* ***Image 3:*** ***S*** *shuttle sutures pulled through bonne tunnels after drilling,* ***A*** *tendon,* ***C*** *greater tubercle,* ***G*** *tendon gap;* ***Image 4:*** *stitching configuration of main sutures,* ***M*** *superficial and* ***N*** *deep thread of caudal suture,* ***O*** *superficial and* ***P*** *deep thread of cranial suture.*

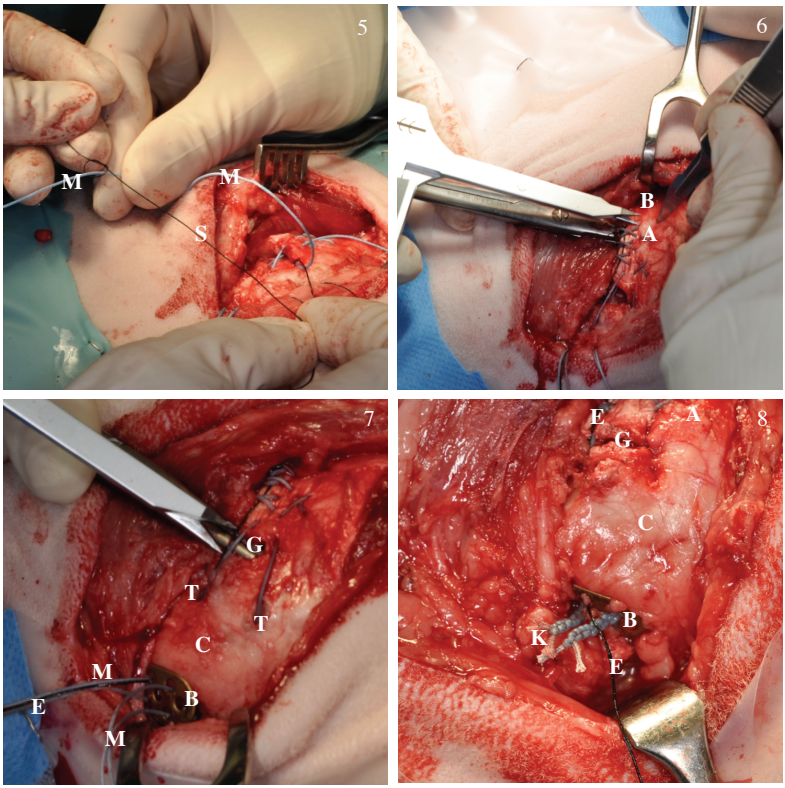

***Image 5**: **M** main sutures tied to **S** shuttle sutures and pulled through bone tunnels; **Image 6**: release cut in **A** proximal tendon between **B** musculotendinous junction and most proximal stitches of caudal suture row; **Image 7:** positioning of **B** button plate slightly proximal to bicipital grove just distal to **C** greater tubercle, **M** main and **E** marking suture threads pulled through plate holes, adjustment of **G** tendon gap to 5mm before knotting, **T** proximal superficial bone tunnel entrances; **Image 8: K** knotted main sutures over **B** plate, **A** tendon, **G** tendon gap, **C** greater tubercle, **E** marking suture.*

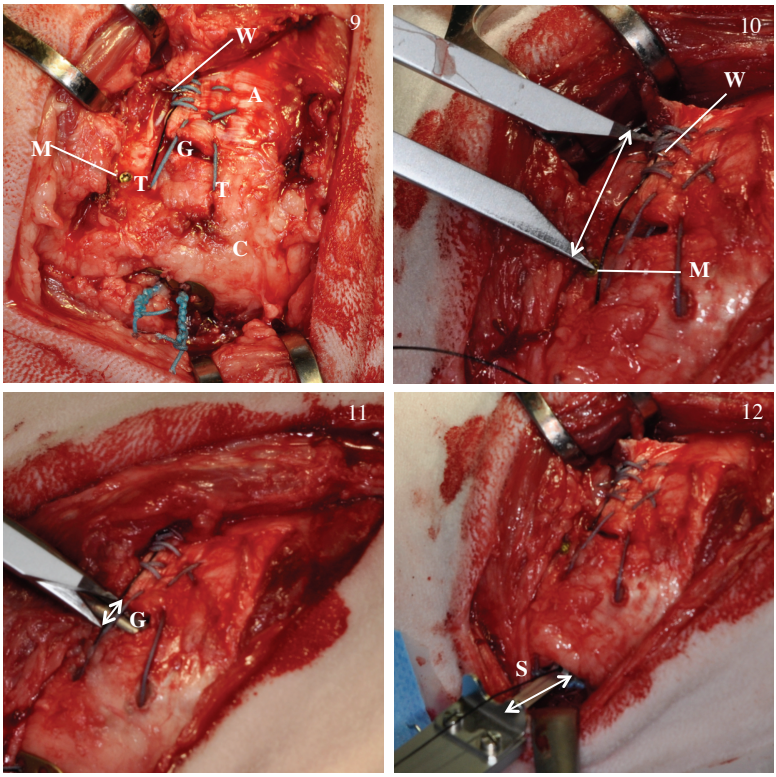

Image 9: *Final repair:* ***A*** *tendon,* ***C*** *greater tubercle,* ***G*** *tendon gap, T proximal superficial tunnel entrances,* ***W*** *steel wire loop,* ***M*** *marking screw:* ***Image 10:*** *Measure* ***A*** *(arrow): distance between* ***W*** *steel wire loop and* ***M*** *marking screw;* ***Image 11****: Measure* ***B*** *(arrow):* ***G*** *gap width at caudal tendon edge (5mm wanted);* ***Image 12****: Measure* ***C*** *(arrow): length of* ***S*** *marking suture end (cut at 20mm from plate).*

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